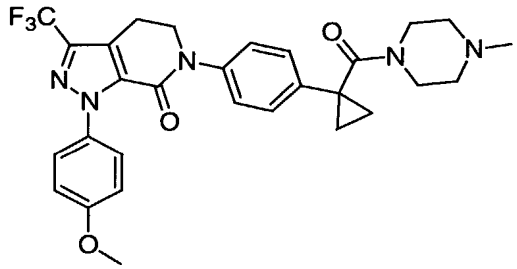
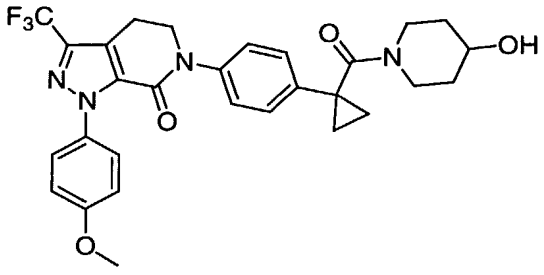
1-(4-methoxyphenyl)-6-(4-{1-[(4-methyl-1-piperazinyl)carbonyl]cyclopropyl}phenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used for the preparation of Example 10, but using 4-methylpiperazine, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS(ESI$^+$) 554.6 $(M+H)^+$, t_R = 4.49 min. HRMS $C_{29}H_{31}O_3F_3N_5$ $(M+H)^+$ 554.2384 calcd for 554.2379. ^{1}H NMR (acetone-d_6) δ 7.50 (d, J = 8.8 Hz, 2H), 7.30 (AA'BB', J = 8.4 Hz, 4H), 6.97 (d, J = 9.1 Hz, 2H), 4.17 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.16 (t, J = 6.4 Hz, 2H), 2.85 (s, 3H), 1.39 (m, 2H), 1.20 (m, 2H) ppm.

Example 13

6-{4-[1-(4-hydroxypiperidine-1-carbonyl)cyclopropyl]phenyl}-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one

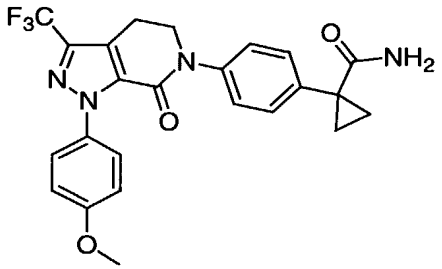


Following a procedure analogous to that used for the preparation of Example 10, but using morpholine, the title compound was prepared. The product was purified by RP-prep

LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS(ESI$^+$) 555.4 $(M+H)^+$, t_R = 5.50 min. HRMS $C_{29}H_{30}O_4F_3N_4$ $(M+H)^+$ 555.2241 calcd for 555.2219.

Example 14

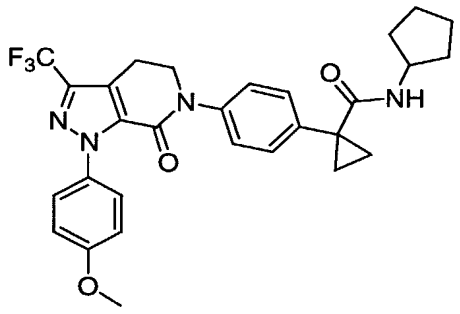
1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropanecarboxamide



Following a procedure analogous to that used for the preparation of Example 10, but using concentrated NH_4OH as the amine source and THF as solvent, the title compound was prepared. The product was purified by prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS(ESI$^+$) 471.6 $(M+H)^+$, t_R = 2.56 min (10-90% CH_3CN/H_2O in a 10-min run). ^1H NMR (acetone-d_6) δ 7.50 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 4.18 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.17 (t, J = 6.6 Hz, 2H), 1.40 (m, 2H), 0.96 (m, 2H) ppm. ^{19}F NMR (acetone-d_6) δ -77.14 ppm.

Example 15

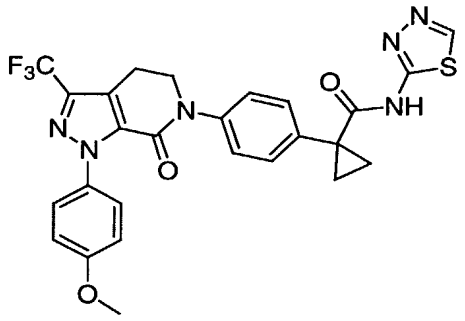
1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropanecarboxylic acid cyclopentylamide



Following a procedure analogous to that used for the preparation of Example 10, but using cyclopentylamine, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS(ESI$^+$) 539.4 $(M+H)^+$, t_R = 6.65 min. ^1H NMR (acetone-d_6) δ 7.51 (d, J = 8.8 Hz, 2H), 7.37 (m, 4H), 6.99 (d, J = 8.8 Hz, 2H), 4.16 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 4.05 (m, 1H), 3.16 (t, J = 6.2 Hz, 2H), 1.79 (m, 2H), 1.45 (m, 4H), 1.22 (m, 2H), 1.39 (m, 2H), 0.92 (m, 2H) ppm.

Example 16

1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}-*N*-(1,3,4-thiadiazol-2-yl)cyclopropanecarboxamide

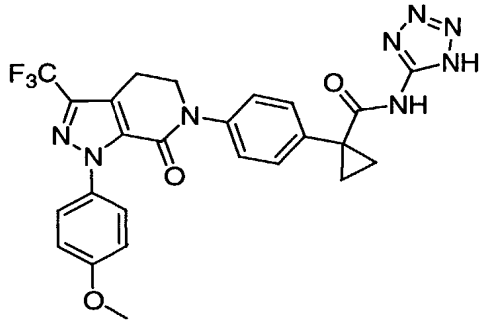


Following a procedure analogous to that used for the preparation of Example 10, but using 2-aminothiadiazole, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS(ESI$^+$) 555.4 $(M+H)^+$, t_R = 6.17 min. ^1H NMR (acetone-d_6) δ 8.96 (s, 1H), 7.54 (m, 4H), 7.43 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.9 Hz, 2H), 4.22 (t, J = 6.6 Hz, 2H), 3.84

(s, 3H), 3.16 (t, J = 6.2 Hz, 2H), 1.67 (m, 2H), 1.31 (m, 2H) ppm.

Example 17

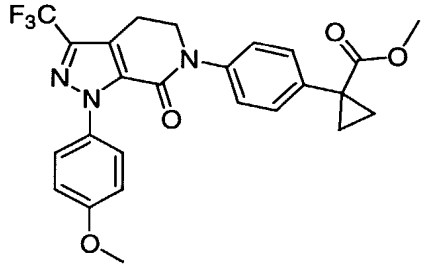
1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}-*N*-(1*H*-tetraazol-5-yl)cyclopropanecarboxamide



Following a procedure analogous to that used for the preparation of Example 10, but using 5-amino-1*H*-tetrazole, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS(ESI$^+$) 539.6 (M+H), t_R = 5.86 min. ^{1}H NMR (acetone-d_6) δ 7.53 (m, 4H), 7.39 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 9.1 Hz, 2H), 4.20 (t, J = 6.6 Hz, 2H), 3.84 (s, 3H), 3.18 (t, J = 6.6 Hz, 2H), 1.68 (m, 2H), 1.29 (m, 2H) ppm.

Example 18

methyl 1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropanecarboxylate

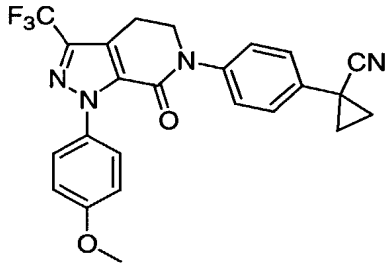


The product from part D in Example 1 (mg, mmol) was stirred in anhydrous MeOH (5 mL) at RT. Catalytic amount of conc.

HCl was added. The resulting solution was stirred at RT overnight. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS(ESI$^+$) 486.6 $(M+H)^+$, t_R = 2.98 min (10-90% CH_3CN/H_2O in a 4-min run). ^1H NMR (acetone-d_6) δ 7.50 (d, J = 8.8 Hz, 2H), 7.35 (AA'BB', J = 8.8 Hz, 4H), 6.97 (d, J = 9.1 Hz, 2H), 4.18 (t, J = 6.6 Hz, 2H), 3.82 (s, 3H), 3.55 (s, 3H), 3.17 (t, J = 6.4 Hz, 2H), 1.49 (m, 2H), 1.16 (m, 2H) ppm.

Example 19

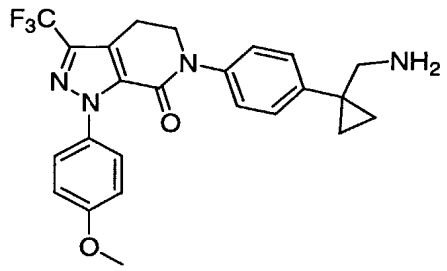
1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropanecarbonitrile



The product from Example 14 (22 mg, 0.047 mmol) was stirred in DMF (0.3 mL) at RT in a capped vial. $SOCl_2$ (0.05 mL) was added. The mixture was stirred at RT for 1.5 h. LC-MS showed completion of the reaction. Prep LC-MS purification (35-98% CH_3CN in H_2O) provided the title compound (15 mg, yield, 71%). LC/MS(ESI$^+$) 453.4 $(M+H)^+$, t_R = 5.24 min. ^1H NMR (acetone-d_6) δ 7.50 (d, J = 9.2 Hz, 2H), 7.39 (m, 4H), 6.97 (d, J = 8.8 Hz, 2H), 4.18 (t, J = 6.6 Hz, 2H), 3.84 (s, 3H), 3.17 (t, J = 6.6 Hz, 2H), 1.71 (m, 2H), 1.48 (m, 2H) ppm. ^{19}F NMR (acetone-d_6) δ -77.16 ppm.

Example 20

6-{4-[1-(aminomethyl)cyclopropyl]phenyl}-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



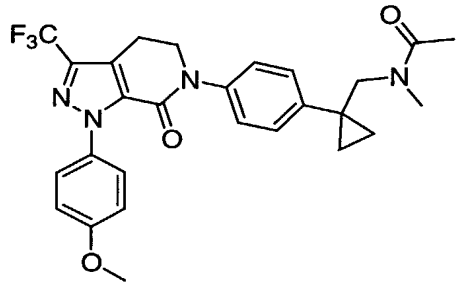
Part A. The product from part E in Example 1 (24 mg, 0.052 mmol) was stirred in CH_2Cl_2 (1 mL) at 0°C under N_2. Et_3N (11 μL, 1.5 eq) was added followed by the dropwise addition of MsCl (4.5 μL, 1.1 eq). The mixture was stirred at 0°C for 1 h. TLC showed completion of the reaction. Sat'd NH_4Cl was added. The mixture was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was dissolved in DMF (1 mL). NaN_3 (50 mg, mmol) was added. The mixture was stirred at RT under N_2 overnight. LC-MS showed the azide as the major component in the mixture. Sat'd NH_4Cl was then added. The mixture was extracted with EtOAc. And the organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated to dryness to give crude 6-{4-[1-azidomethylcyclopropyl]phenyl}-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one. LC/MS(ESI$^+$) 483.4 $(M+H)^+$, t_R = 3.06 min (10-90% CH_3CN in H_2O in a 4-min run).

Part B. The product from part A (18 mg) and PPh_3 (38 mg) were stirred in THF (1.5 mL) at RT for 20 min. H_2O (0.3 mL) was added, and the mixture was stirred at 30°C for 2 h. The solvents were evaporated. The residue was purified by prep LC-MS (5-98%CH_3CN in H_2O) to give pure 6-{4-[1-(aminomethyl)cyclopropyl]phenyl}-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-

c]pyridin-7-one(7 mg, yield: 29%). LC/MS(ESI$^+$) 457.4 $(M+H)^+$.

Example 21

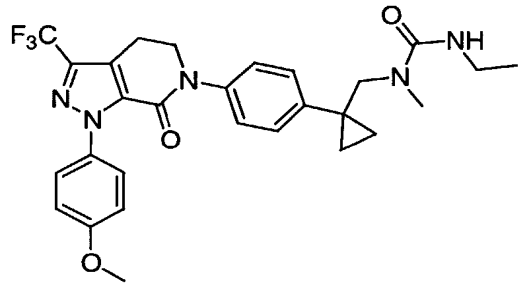
_N_-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6_H_-pyrazolo[3,4-_c_]pyridin-6-yl]phenyl}cyclopropyl)methyl]-_N_-methylacetamide



The product of Example 1 (40 mg, 0.084 mmol) was stirred in CH_2Cl_2 (1 mL) in a capped vial at RT. Et_3N (4 drops) was added followed by addition of acetyl chloride (2 drops). The resulting mixture was stirred at RT for 10 min. LC-MS showed completion of the reaction. After evaporation of the solvents, the residue was dissolved in MeOH (1 mL) and purified by prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run) to afford pure *N*-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropyl)methyl]-*N*-methylacetamide (35 mg, yield: 80.3%). LC/MS(ESI$^+$) 513.4 $(M+H)^+$, t_R = 6.08 min. HRMS $C_{27}H_{28}O_3F_3N_4$ $(M+H)^+$ 513.2120 calcd for 513.2113. ^1H NMR (acetone-d_6) δ 7.49 (d, J = 9.1 Hz, 2H), 7.33 (m, 4H), 6.97 (d, J = 9.0 Hz, 2H), 4.15 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.58 (s, 1H), 3.49 (s, 1H), 3.16 (t, J = 6.6 Hz, 2H), 2.91, 2.80 (2 x s, 3H), 1.89, 1.50 (2 x s, 3H), 0.87 (m, 2H), 0.78 (m, 2H) ppm.

Example 22

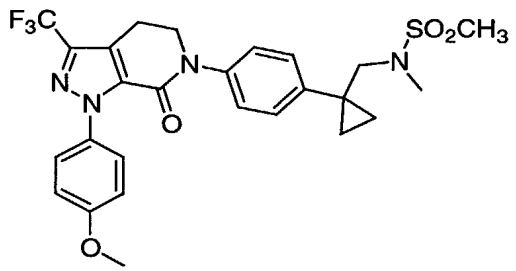
***N'*-ethyl-*N*-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropyl)methyl]-*N*-methylurea**



The product of Example 1 (20 mg, 0.042 mmol) was stirred in CH_2Cl_2 (1 mL) in a capped vial at RT. Et_3N (4 drops) was added followed by addition of ethyl isocyanide (2 drops). The resulting mixture was stirred at RT for 2 h. LC-MS showed completion of the reaction. After evaporation of the solvents, the residue was dissolved in MeOH (1 mL), and purified by prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run) to afford pure *N'*-ethyl-*N*-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropyl)methyl]-*N*-methylurea (16 mg, yield: 70%). HRMS $C_{28}H_{31}O_3F_3N_5$ 542.2370 (M+H), calcd for 542.2380. ^1H NMR (acetone-d_6) δ 7.49 (d, J = 9.2 Hz, 2H), 7.30 (AA'BB', J = 8.4 Hz, 4H), 6.97 (d, J = 8.8 Hz, 2H), 4.14 (t, J = 6.3 Hz, 2H), 3.82 (s, 3H), 3.51 (s, 2H), 3.16 (t, J = 6.4 Hz, 2H), 3.02 (q, J = 7.0 Hz, 2H), 2.70 (s, 3H), 0.92 (t, J = 7.0 Hz, 3H), 0.86 (m, 2H), 0.76 (m, 2H) ppm.

Example 23

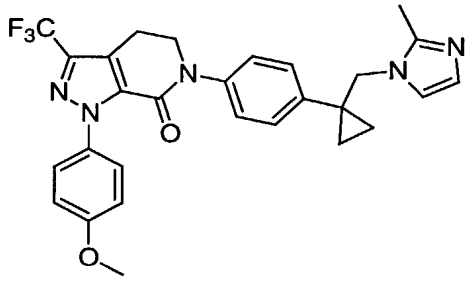
***N*-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropyl)methyl]-*N*-methylmethanesulfonamide**



The product of Example 1 (20 mg, 0.042 mmol) was stirred in CH_2Cl_2 (1 mL) in a capped vial at RT. Pyridine (4 drops) was added followed by two drops of methanesulfonyl chloride. The resulting mixture was stirred for 20 min. LC-MS showed completion of the reaction. After evaporation of the solvents, the residue was dissolved in MeOH (1 mL), and purified by prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run) to afford pure *N*-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropyl)methyl]-*N*-methylmethanesulfonamide (16 mg, yield: 69%). LC/MS(ESI$^+$) 549.4 $(M+H)^+$, t_R = 6.40 min.

Example 24

1-(4-methoxyphenyl)-6-{4-[1-(2-methylimidazol-1-ylmethyl)cyclopropyl]phenyl}-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one



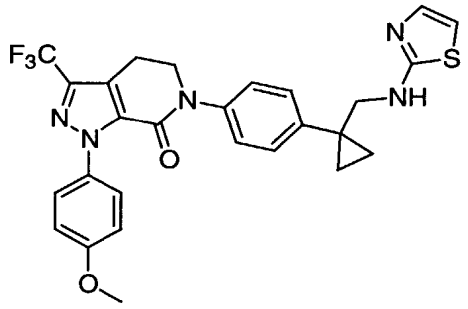
Part A. The product of part E in Example 1 (0.45 g, 0.98 mmol) was stirred in CH_2Cl_2 (10 mL) at 0°C under N_2. PPh_3 (0.52 g, 2.0 eq) was added, followed by the addition of CBr_4 (0.33 g, 1.0 eq). The resulting mixture was stirred at 0°C for 30 min. LC-MS showed completion of the reaction. The mixture was extracted with EtOAc. The

organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated to dryness. It was used directly in the next step without purification. LC/MS(ESI$^+$) 520.4, 522.4 $(M+H)^+$.

Part B. The product of Part A (0.20 g, 0.38 mmol), 2-methylimidazole (0.10 g, 1.22 mmol), and K_2CO_3 (0.25 g, 3.62 mmol) were stirred in DMF (0.4 mL) at RT under N_2. The mixture was heated at 85-90°C for 30 min. LC-MS showed completion of the reaction. After cooling to RT, H_2O was added. The mixture was purified by prep LC-MS (35-98% CH_3CN in H_2O) to give pure 1-(4-methoxyphenyl)-6-{4-[1-(2-methylimidazol-1-ylmethyl)cyclopropyl]phenyl}-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one (53 mg, yield: 27%). LC/MS(ESI$^+$) 522.4 $(M+H)^+$. ^1H NMR (acetone-d_6) δ 7.53 (m, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.39 (m, 1H), 7.25 (AA'BB', J = 8.4 Hz, 4H), 6.98 (d, J = 8.8 Hz, 2H), 4.38 (s, 2H), 4.15 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.14 (t, J = 6.6 Hz, 2H), 2.10 (s, 3H), 1.26 (t, J = 5.5 Hz, 2H), 1.02 (t, J = 5.5 Hz, 2H) ppm.

Example 25

1-(4-methoxyphenyl)-6-{4-[1-(thiazol-2-ylaminomethyl)-cyclopropyl]phenyl}-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one

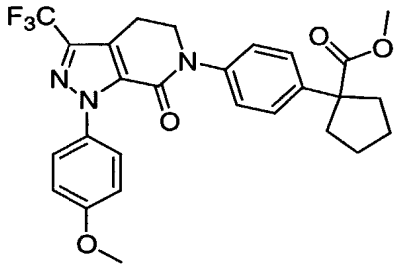


Following a procedure analogous to that of Example 24, the title compound was prepared by using 2-aminothiazole. The

product was purified by RP-prep LC-MS (35-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 540.6 $(M+H)^+$, t_R = 3.37 min.

Example 26

methyl 1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopentanecarboxylate



Part A. 1-Phenyl-cyclopentylcarboxylic acid (3.0 g, 15.8 mmol) was stirred in HOAc (10 mL) at RT under N_2. I_2 (4.01 g, 15.8 mmol) was added followed by the addition of $NaIO_3$ (0.78 g, 3.94 mmol) and conc. H_2SO_4 (0.3 mL). The resulting mixture was stirred at 70°C for 3 days. The cooled mixture was poured into H_2O, and extracted with EtOAc. The organic layer was washed with sodium thiosulfate and brine, dried over $MgSO_4$, filtered, and concentrated to dryness to yield 4-iodophenylcylcopentylcarboxylic acid (4.45 g, yield: 89%). LC/MS(ESI^+) 317.6 $(M+H)^+$.

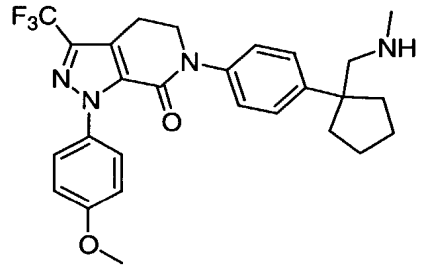
Part B. The product from part A (1.08 g, 3.43 mmol) and 1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (0.82 g, 2.64 mmol) were stirred in DMSO (3 mL) under N_2. K_2CO_3 (1.09 g, 7.90 mmol, 3.0 eq) was added followed by the addition of 1,10-phenanthroline (96 mg, 20 mol%) and CuI (100 mg, 20mol%). The resulting mixture was stirred at 130°C for 5h. LC-MS showed completion of the reaction. It was acidified with 1N HCl, and extracted with EtOAc (2x). The organic layer was washed with H_2O, brine, dried over $MgSO_4$, filtered, and concentrated to afford 1-{4-[1-(4-methoxyphenyl)-7-oxo-3-

(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopentanecarboxylic acid (1.30 g, yield: 99%). LC/MS(ESI$^+$) 500.6 $(M+H)^+$.

Part C. The product of part B (40 mg, 0.080 mmol) was dissolved in MeOH (5 mL), and conc. HCl (0.5 mL) was added. The resulting mixture was stirred at 60°C overnight. After cooling, the mixture was purified by prep LC-MS (35-98% CH_3CN in H_2O in a 10-min run) to afford methyl 1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopentane carboxylate (32 mg, yield: 78%). LC/MS(ESI$^+$) 514.6 $(M+H)^+$, t_R = 6.09 min. ^1H NMR ($CDCl_3$) δ 7.45 (d, J = 8.8 Hz, 2H), 7.30 (AA'BB', J = 8.6 Hz, 4H), 6.92 (d, J = 9.0 Hz, 2H), 4.13 (t, J = 6.8 Hz, 2H), 3.81 (s, 3H), 3.39 (s, 3H), 3.15 (t, J = 6.6 Hz, 2H), 2.65-2.58 (m, 2H), 1.89-1.82 (m, 2H), 1.73-1.69 (m, 4H), 1.58 (m, 2H) ppm.

Example 27

1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclopentyl}phenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Part A. The product from part B of Example 26 (1.46 g, 2.93 mmol) was stirred in THF (10 mL) at 0°C under N_2. Et_3N (0.62 mL, 4.40 mmol, 1.5 eq) was added followed by dropwise addition of $ClCO_2Et$ (0.31 mL, 3.24 mmol, 1.1 eq). The reaction mixture was then stirred at 0°C for 1 h. TLC

showed completion of the reaction. The mixture was filtered, and rinsed with anhydrous THF. The THF filtrate (ca. 20 mL) was stirred at 0°C under N_2. MeOH (5 mL) was added followed by the addition of $NaBH_4$ (1.03 g, 27.10 mmol, 9.3 eq). The resulting mixture was stirred at 0°C for 40 min. Analytical LC-MS showed completion of the reaction. Sat'd Na_2SO_4 was then added. The mixture was extracted with EtOAc (2x). The organic layer was washed with H_2O (2x) and brine (2x), dried over Na_2SO_4, filtered, and concentrated to dryness to give 6-{4-[1-(hydroxymethyl)cyclopentyl]phenyl}-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (1.38 g, 97%). LC/MS (ESI^+) 486.4 $(M+H)^+$.

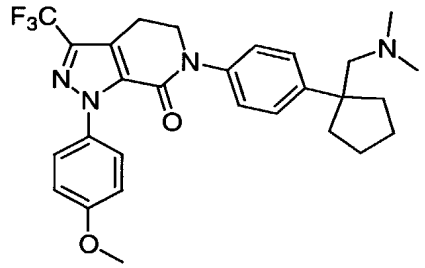
Part B. The product from part A (0.80 g, 1.65 mmol) was stirred in anhydrous CH_2Cl_2 (10 mL) at RT under N_2. NaOAc (0.5 g, 6.10 mmol) and molecular sieves (4Å, 1.2 g) were added followed by the addition of PCC (0.89 g, 4.12 mmol). The resulting slurry was stirred at RT for 4 h. Analytical LC-MS showed completion of the reaction. The mixture was filtered, and rinsed with CH_2Cl_2. The filtrate was washed with H_2O (2x) and brine (2x), dried over Na_2SO_4, filtered, and concentrated to dryness to afford 1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopentanecarbaldehyde (0.78 g, yield: 99%). LC/MS (ESI^+) 484.6 $(M+H)^+$.

Part C. The product from part B (100 mg, 0.21 mmol) and methylamine hydrochloride (100 mg, excess) were stirred in dichloroethane (1.0 mL) in a capped vial. $NaBH(OAc)_3$ (200 mg, 0.94 mmol) was added followed by addition of three drops of HOAc. The reaction mixture was stirred at RT for 2h. Analytical LC-MS showed completion of the reaction. The mixture was evaporated and dissolved in aqueous MeOH.

It was then purified by prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run) to obtain 1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclopentyl}phenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (35 mg, yield: 34%). LC/MS (ESI^+) 499.4 $(M+H)^+$, t_R = 4.85 min. ^1H NMR (acetone-d_6) δ 7.50 (m, 4H), 7.35 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 9.1 Hz, 2H), 4.17 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 3H), 3.39 (s, 2H), 3.16 (t, *J* = 6.3 Hz, 2H), 2.64 (s, 3H), 2.14-1.66 (m, 8H) ppm.

Example 28

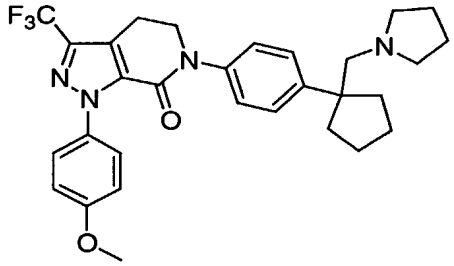
6-(4-{1-[(dimethylamino)methyl]cyclopentyl}phenyl)-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used for Example 27, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 513.6 $(M+H)^+$, t_R = 4.96 min. ^1H NMR (acetone-d_6) δ 7.52 (m, 4H), 7.38 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.19 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 3H), 3.60 (s, 2H), 3.17 (t, *J* = 6.3 Hz, 2H), 2.62 (s, 6H), 2.16-1.64 (m, 8H) ppm.

Example 29

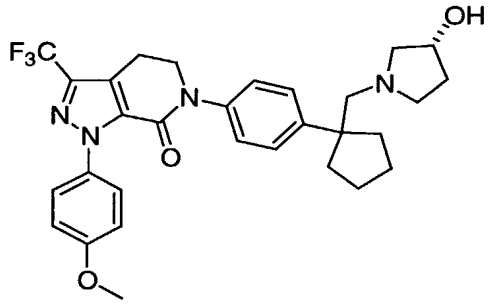
1-(4-methoxyphenyl)-6-{4-[1-(1-pyrrolidinylmethyl)cyclopentyl]phenyl}-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used for Example 27, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 539.6 $(M+H)^+$, t_R = 5.13 min. ^1H NMR (acetone-d_6) δ 7.52 (m, 4H), 7.40 (d, J = 8.1 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 4.19 (t, J = 6.3 Hz, 2H), 3.83 (s, 3H), 3.75 (s, 2H), 3.52 (m, 2H), 3.17 (t, J = 6.3 Hz, 2H), 2.92 (m, 2H), 2.18 (m, 2H), 2.04-1.62 (m, 10H) ppm. ^{19}F NMR (acetone-d_6) δ -62.17 (TFA salt), -79.82 (CF_3) ppm.

Example 30

6-[4-(1-{[(3*R*)-3-hydroxy-1-pyrrolidinyl]methyl}cyclopentyl)phenyl]-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt

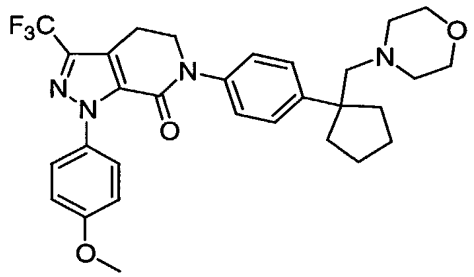


Following a procedure analogous to that used for Example 27, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 555.6 $(M+H)^+$, t_R = 4.77 min. ^1H NMR (acetone-d_6) δ 7.52 (m, 4H), 7.40 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 4.36 (s, br, 1H), 4.19 (t, J = 6.3 Hz, 2H), 3.83 (s, 3H), 3.72 (m, 2H), 3.59 (m, 2H), 3.17 (t, J = 6.3

Hz, 2H), 2.92 (m, 2H), 2.16-1.63 (m, 10H) ppm. ^{19}F NMR (acetone-d_6) δ -62.16 (TFA salt), -76.70 (CF_3) ppm.

Example 31

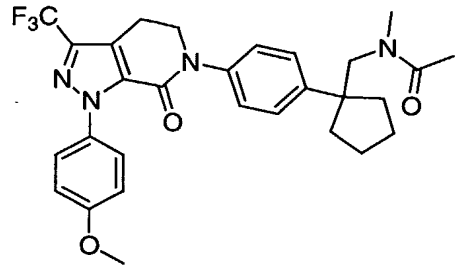
1-(4-methoxyphenyl)-6-{4-[1-(4-morpholinylmethyl)cyclopentyl]phenyl}-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used for Example 27, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI$^+$) 555.6 $(M+H)^+$, t_R = 4.49 min. ^1H NMR (acetone-d_6) δ 7.43 (m, 4H), 7.28 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 4.09 (t, J = 6.6 Hz, 2H), 3.74 (s, 3H), 3.65 (m, 4H), 3.50 (s, 2H), 3.33 (m, 2H), 3.07 (t, J = 6.3 Hz, 2H), 2.89 (m, 2H), 2.02-1.52 (m, 8H) ppm.

Example 32

***N*-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopentyl)methyl]-*N*-methylacetamide**

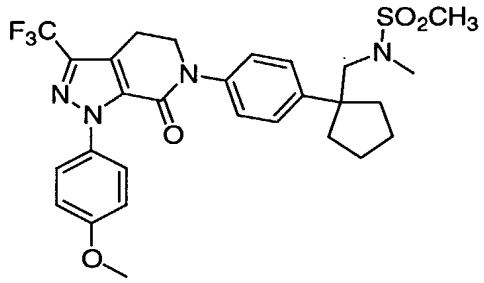


Following a procedure analogous to that used for Example 21, the title compound was prepared. The product was

purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 541.6 $(M+H)^+$, t_R = 6.50 min. ^1H NMR (acetone-d_6) δ 7.49 (dd, J = 8.8, 1.8 Hz, 2H), 7.34 (m, 4H), 6.97 (dd, J = 8.8, 1.8 Hz, 2H), 4.17 (t, J = 6 Hz, 2H), 3.82 (s, 3H), 3.52 (s, 2H), 3.17 (t, J = 6 Hz, 2H), 2.34 (s, 3H), 2.03-1.59 (m, 11H) ppm.

Example 33

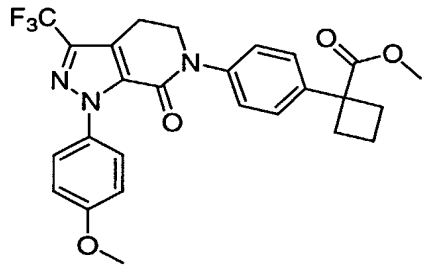
***N*-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopentyl)methyl]-*N*-methylmethanesulfonamide**



Following a procedure analogous to that used for Example 23, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 577.4 $(M+H)^+$, t_R = 6.74 min. ^1H NMR (acetone-d_6) δ 7.50 (d, J = 9 Hz, 2H), 7.35 (m, 4H), 6.98 (d, J = 9 Hz, 2H), 4.18 (t, J = 6.5 Hz, 2H), 3.83 (s, 3H), 3.22 (s, 2H), 3.17 (t, J = 6.5 Hz, 2H), 2.70 (s, 3H), 2.17 (s, 3H), 2.13 (m, 2H), 1.80 (m, 4H), 1.64 (m, 2H) ppm.

Example 34

methyl 1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclobutanecarboxylate



Part A. 1-Phenyl-1-cyclobutylcarbonitrile (5.0 g, 31.83 mmol) and KOH (85%, 6.29 g, 95.49 mmol, 3 eq) were heated in ethylene glycol (10 mL) at 185-190°C for 6h under N_2. LC-MS showed completion of the reaction. H_2O was added to the cooled mixture. It was extracted with Et_2O (3x). The aqueous layer was acidified with conc. HCl, and then extracted with $CHCl_3$ (2x). The chloroform layer was washed with H_2O, brine, dried over $MgSO_4$, filtered, and concentrated to dryness to give 1-phenyl-1-cyclobutyl carboxylic acid (4.43 g, yield: 79.2%). LC/MS (ESI^+) 177.4 $(M+H)^+$, t_R = 2.56 min (10-90% CH_3CN/H_2O in a 6-min run).

Part B. The product from part A (4.43 g, 25.2 mmol) was stirred in HOAc (20 mL) at RT under N_2. I_2 (6.40 g, 25.2 mmol) was added, followed by the addition of $NaIO_3$ (1.25 g, 6.3 mmol) and conc. H_2SO_4 (0.5 mL). The resulting mixture was stirred at 70°C for 2 days. LC-MS showed completion of the reaction. The cooled mixture was poured into H_2O, and extracted with EtOAc. The organic layer was washed with sodium thiosulfate, brine, dried over $MgSO_4$, filtered, and concentrated to dryness to give 4-iodophenylcylcobutyl carboxylic acid (6.49 g, 85%). LC/MS (ESI^+) 303.2 $(M+H)^+$, t_R = 2.55 min (10-90% CH_3CN/H_2O in a 4-min run).

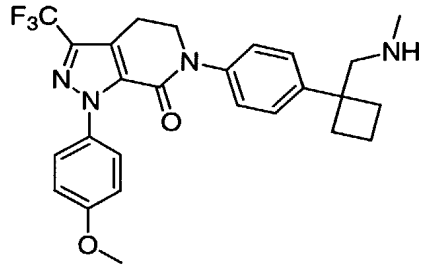
Part C. The product from part B (1.20 g, 3.97 mmol) and 1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (0.87 g, 2.8 mmol) were stirred in DMSO (3 mL) under N_2. K_2CO_3 (1.16 g, mmol, 3.0

eq) was added followed by the addition of 1,10-phenanthroline (100 mg, 20 mol%) and CuI (106 mg, 20 mol%). The resulting mixture was stirred at 130°C overnight. LC-MS showed completion of the reaction. EtOAc was added to the cooled solution. The solution was acidified with 1N HCl, and the organic layer was washed with H_2O and and brine, dried over $MgSO_4$, filtered, and concentrated to afford 1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclobutane carboxylic acid (1.34 g, yield 97%). LC/MS (ESI^+) 486.6 $(M+H)^+$, t_R = 2.81 min (10-90% CH_3CN/H_2O in a 4-min run).

Part D. The product from part C (50 mg, 0.103 mmol) was dissolved in MeOH (5 mL), and conc. HCl (0.5 mL) was added. The resulting mixture was stirred at reflux for 2 h. After cooling, the mixture was purified by prep LC-MS (35-98% CH_3CN in H_2O) to afford the title compound (35 mg, yield: 68%). LC/MS (ESI^+) 499.4 $(M+H)^+$, t_R = 5.70 min. ^1H NMR ($CDCl_3$) δ 7.45 (d, *J* = 8.8 Hz, 2H), 7.28 (AA'BB', *J* = 8Hz, 4H), 6.91 (d, *J* = 8.8 Hz, 2H), 4.13 (t, *J* = 6.9 Hz, 2H), 3.80 (s, 3H), 3.63 (s, 3H), 3.15 (t, *J* = 6.6 Hz, 2H), 2.81 (m, 2H), 2.48 (m, 2H), 2.03 (m, 1H), 1.86 (m, 1H) ppm.

Example 35

1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclobutyl}phenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



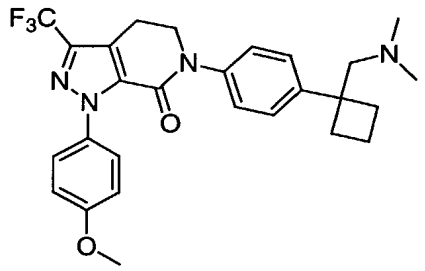
Part A. The product from part C of Example 34 (1.32 g, 2.72 mmol) was stirred in THF (10 mL) at 0°C under N_2. Et_3N (0.59 mL, 4.08 mmol, 1.5 eq) was added followed by dropwise addition of $ClCO_2Et$ (0.38 mL, 3.54 mmol, 1.3 eq). The reaction mixture was then stirred at 0°C for 30 min. TLC showed completion of the reaction. The mixture was filtered and rinsed with anhydrous THF. The THF filtrate (ca. 20 mL) was stirred at 0°C under N_2. MeOH (4 mL) was added followed by the addition of $NaBH_4$ (1.03 g, 27.10 mmol, 10 eq). The resulting mixture was stirred at 0°C for 40 min. Analytical LC-MS showed completion of the reaction. Sat'd Na_2SO_4 was then added. The mixture was extracted with EtOAc (2x). The organic layer was washed with H_2O(2x) and brine (2x), dried over Na_2SO_4, filtered, and concentrated to dryness to give 6-{4-[1-(hydroxymethyl)cyclobutyl]phenyl}-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (1.30 g, 99%). LC/MS (ESI^+) 472.6 $(M+H)^+$, t_R = 2.84 min (10-90% CH_3CN/H_2O in a 4-min run).

Part B. The product from part A (0.90 g, 1.91 mmol) was stirred in anhydrous CH_2Cl_2 (10 mL) at RT under N_2. NaOAc (0.32 g, 3.82 mmol, 2.0 eq) and molecular sieves (4A, 0.90 g) were added followed by the addition of PCC (0.69 g, 2.87 mmol, 1.5 eq). The resulting slurry was stirred at RT for 4 h. Analytical LC-MS showed completion of the reaction. The mixture was filtered and rinsed with CH_2Cl_2. The filtrate was washed with H_2O (2x) and brine (2x), dried over Na_2SO_4, filtered, and concentrated to dryness to afford 1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclobutanecarbaldehyde (0.88 g, yield: 99%). LC/MS (ESI^+) 470.6 $(M+H)^+$, t_R = 3.01 min (10-90% CH_3CN/H_2O in a 4-min run).

Part C. The product from part B (500 mg, 1.04 mmol), methylamine hydrochloride (200 mg, excess) were stirred in dichloroethane (15 mL) at RT under N_2. $NaBH(OAc)_3$ (1.03 g, 4.86 mmol) was added followed by addition of three drops of HOAc. The reaction mixture was stirred at RT for 2.5 h. Analytical LC-MS showed completion of the reaction. The mixture was evaporated, and dissolved in aqueous MeOH. It was then purified by prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run) to obtain 1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclobutyl}phenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (230 mg, 46%). LC/MS (ESI^+) 485.4 $(M+H)^+$, t_R = 4.93 min. ^1H NMR (acetone-d_6) δ 7.51 (d, 2H), 7.33 (m, 4H), 6.99 (d, 2H), 4.17 (m, 2H), 3.83 (s, 3H), 3.62 (m, 2H), 3.17 (m, 2H), 2.73 (s, 3H), 2.46 (m, 4H), 2.15-1.86 (m, 2H) ppm. ^{19}F NMR (acetone-d_6) δ -62.18 (TFA), -76.65 (CF_3) ppm.

Example 36

6-(4-{1-[(dimethylamino)methyl]cyclobutyl}phenyl)-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt

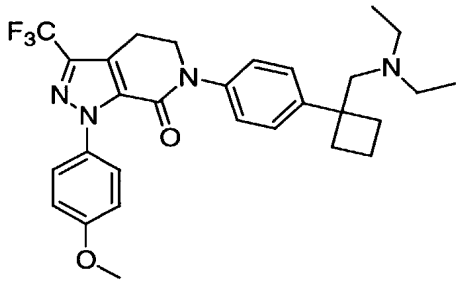


Following a procedure analogous to that used for Example 35, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 499.6 $(M+H)^+$, t_R = 4.75 min. ^1H NMR (acetone-d_6) δ 7.49 (m, 4H), 7.39 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* =

9.1 Hz, 2H), 4.19 (t, J = 6.4 Hz, 2H), 3.83 (s, 3H), 3.77 (m, 2H), 3.17 (t, J = 6.3 Hz, 2H), 2.68 (s, 6H), 2.48 (t, J = 7.5 Hz, 4H), 2.09 (m, 1H), 1.89 (m, 1H) ppm.

Example 37

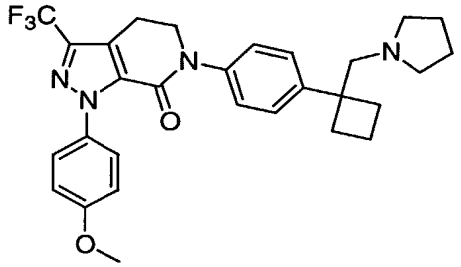
6-(4-{1-[(diethylamino)methyl]cyclobutyl}phenyl)-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used for Example 35, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI$^+$) 527.6 $(M+H)^+$, t_R = 5.04 min. ^1H NMR (acetone-d_6) δ 7.53 (m, 4H), 7.39 (d, J = 8.5 Hz, 4H), 6.98 (d, J = 9.1 Hz, 2H), 4.19 (t, J = 6.3 Hz, 2H), 3.83 (s, 3H), 3.68 (s, 2H), 3.17 (t, J = 6.3 Hz, 2H), 2.95 (m, 4H), 2.48 (t, J = 7.8 Hz, 4H), 2.10-1.85 (m, 2H), 1.16 (m, 6H) ppm.

Example 38

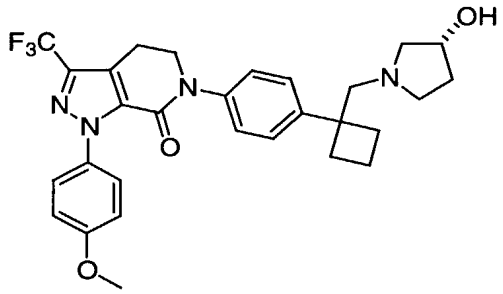
1-(4-methoxyphenyl)-6-{4-[1-(1-pyrrolidinylmethyl)cyclobutyl]phenyl}-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used for Example 35, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 525.6 $(M+H)^+$, t_R = 4.97 min. ^1H NMR (acetone-d_6) δ 7.51 (d, J = 8.4 Hz, 2H), 7.39 (m, 4H), 6.98 (d, J = 8.8 Hz, 2H), 4.19 (t, J = 6.4 Hz, 2H), 3.87 (m, 2H), 3.83 (s, 3H), 3.51 (m, 2H), 3.17 (t, J = 6.3 Hz, 2H), 2.93 (m, 2H), 2.47 (m, 4H), 2.09-1.85 (m, 6H) ppm. ^{19}F NMR (acetone-d_6) δ -62.16 (TFA), -76.74 (CF_3) ppm.

Example 39

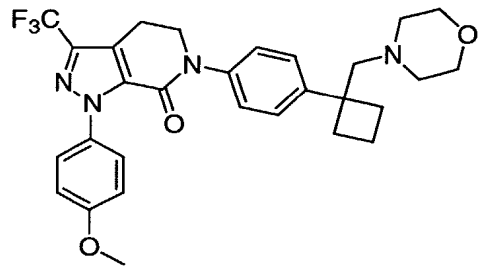
6-[4-(1-{[(3*R*)-3-hydroxy-1-pyrrolidinyl]methyl}cyclobutyl)phenyl]-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used for Example 35, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 541.6 $(M+H)^+$, t_R = 4.77 min. ^1H NMR (acetone-d_6) δ 7.51 (d, J = 8.9 Hz, 2H), 7.39 (m, 4H), 6.98 (d, J = 9.1 Hz, 2H), 4.33 (m, 1H), 4.20 (t, J = 6.5 Hz, 2H), 3.83 (m, 7H), 3.52 (m, 2H), 3.17 (t, J = 6.5 Hz, 2H), 2.47 (m, 4H), 2.14-1.84 (m, 4H). ^{19}F NMR (acetone-d_6) δ -62.16 (TFA), -76.34 (CF_3) ppm.

Example 40

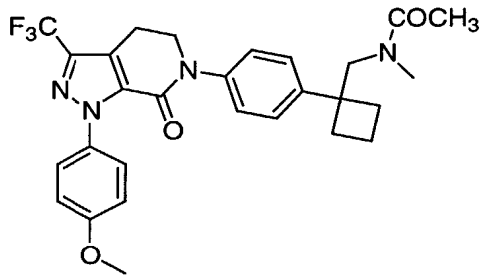
1-(4-methoxyphenyl)-6-{4-[1-(4-morpholinylmethyl)cyclobutyl]phenyl}-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used for Example 35, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 541.6 $(M+H)^+$, t_R = 4.86 min. ^1H NMR (acetone-d_6) δ 7.49 (m, 4H), 7.37 (m, 2H), 6.98 (d, J = 8.8 Hz, 2H), 4.18 (m, 2H), 3.83 (s, 3H), 3.74 (m, 8H), 3.17 (t, J = 6.5 Hz, 2H), 3.00 (m, 2H), 2.46 (m, 4H), 1.86 (m, 2H) ppm.

Example 41

***N*-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclobutyl)methyl]-*N*-methylacetamide**

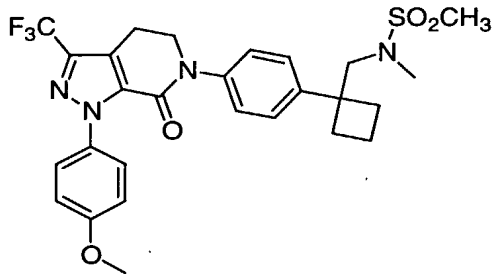


Following a procedure analogous to that used for Example 21, the title compound was prepared by using the product from Example 37 and acetyl chloride as the starting material. The mixture was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 527.2 $(M+H)^+$, t_R = 6.36 min. ^1H NMR (acetone-d_6) δ 7.50 (d, J = 9.2 Hz, 2H),

7.33 (d, J = 8.7 Hz, 2H), 7.24 (m, 2H), 6.98 (d, J = 9.2 Hz, 2H), 4.17 (d, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.71, 3.67 (s, 2H), 3.17 (t, J = 6.5 Hz, 2H), 2.76, 2.45 (s, 3H), 2.35 (m, 2H), 2.18 (m, 1H), 2.08 (m, 1H), 1.76 (m, 2H), 1.33 (m, 1H) ppm.

Example 42

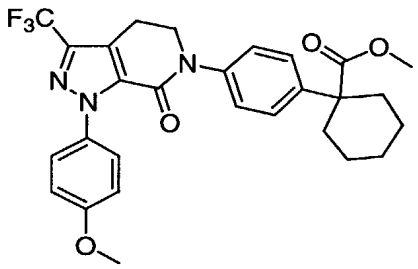
***N*-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclobutyl)methyl]-*N*-methylmethanesulfonamide**



Following a procedure analogous to that used for Example 23, the title compound was prepared. The mixture was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI$^+$) 563.2 $(M+H)^+$, t_R = 6.62 min. ^{1}H NMR (acetone-d_6) δ 7.50 (d, J = 8.8 Hz, 4H), 7.34 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 4.18 (d, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.45 (s, 2H), 3.17 (t, J = 6.5 Hz, 2H), 2.70 (s, 3H), 2.38 (m, 2H), 2.28 (s, 3H), 2.26 (m, 2H), 2.03 (m, 1H), 1.81 (m, 1H) ppm.

Example 43

1-{4-[1-(4-Methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-*c*]pyridin-6-yl]-phenyl}cyclohexanecarboxylic acid methyl ester



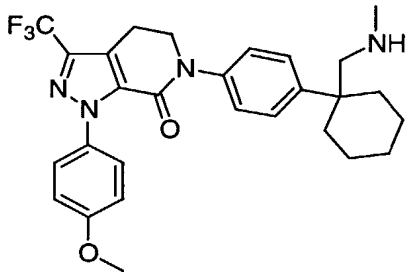
Part A. 1-Phenyl-cyclohexylcarboxylic acid (3.0 g, 14.70 mmol) was stirred in HOAc (10 mL) at RT under N_2. I_2 (3.73 g, 14.70 mmol) was added, followed by the addition of $NaIO_3$ (0.72 g, 3.64 mmol) and conc. H_2SO_4 (0.2 mL). The resulting mixture was stirred at 70°C for 2 days. LC-MS showed the majority was the desired product. After partial evaporation, the cooled mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with sodium thiosulfate and brine, dried over $MgSO_4$, filtered, and concentrated to dryness to give almost pure 4-iodophenylcyclohexylcaroxylic acid (4.56 g, yield: 93.7%). LC/MS (ESI^+) 331.4 $(M+H)^+$, t_R = 3.96 min (10-90% CH_3CN/H_2O in a 6-min run).

Part B. The product of part A (0.70 g, 2.25 mmol) and 1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (0.70 g, 2.25 mmol) were stirred in DMSO (3 mL) under N_2. K_2CO_3 (0.93 g, mmol, 3.0 eq) was added, followed by the addition of 1,10-phenanthroline (80 mg, 20 mmol%) and CuI (85 mg, 20mmol%). The resulting mixture was stirred at 130°C for 2 days. LC-MS showed completion of the reaction. EtOAc was added to the cooled solution. It was acidified with 1N HCl; and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. LC/MS (ESI^+) 514.4 $(M+H)^+$. The residue (50 mg) was dissolved in MeOH (5 mL), and conc. HCl (0.5 mL) was added. The resulting mixture was stirred at 60°C for 4 h. After cooling, the mixture was purified by prep LC-MS (35-98% CH_3CN in H_2O) to give

pure 1-{4-[1-(4-Methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-*c*]pyridin-6-yl]-phenyl}cyclohexanecarboxylic acid methyl ester (43 mg, yield: 83.7%). LC/MS (ESI^+) 528.4 $(M+H)^+$, t_R = 6.38 min. ^1H NMR ($CDCl_3$) δ 7.45 (d, *J* = 9.1 Hz, 2H), 7.32 (AA'BB', *J* = 8.6 Hz, 4H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.13 (t, *J* = 6.6 Hz, 2H), 3.81 (s, 3H), 3.63 (s, 3H), 3.15 (t, *J* = 6.6 Hz, 2H), 2.45 (m, 2H), 1.72-1.24 (m, 8H) ppm.

Example 44

1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclohexyl}phenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Part A. The product from part B of Example 43 (1.34 g, 2.61 mmol) was stirred in THF (10 mL) at 0°C under N_2. Et_3N (0.55 mL, 3.92 mmol, 1.5 eq) was added followed by dropwise addition of $ClCO_2Et$ (0.33 mL, 3.34 mmol, 1.3 eq). The reaction mixture was then stirred at 0°C for 20 min. TLC showed completion of the reaction. The mixture was filtered, and rinsed with anhydrous THF. The THF filtrate (ca. 20 mL) was stirred at 0°C under N_2. MeOH (3.5 mL) was added followed by the addition of $NaBH_4$ (1.00 g, 26.3 mmol, 10 eq). The resulting mixture was stirred at 0°C for 40 min. Analytical LC-MS showed completion of the reaction. Sat'd Na_2SO_4 was then added. The mixture was extracted with EtOAc (2x). The organic layer was washed with H_2O (2x) and brine (2x), dried over Na_2SO_4, filtered, and concentrated to

dryness to give 6-{4-[1-(hydroxymethyl)cyclohexyl]phenyl}-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (1.21 g, yield 92.8%). LC/MS (ESI^+) 500.6 $(M+H)^+$, t_R = 3.06 min (10-90% CH_3CN/H_2O in a 4-min run). ^1H NMR ($CDCl_3$) δ 7.46 (d, *J* = 8.8 Hz, 2H), 7.34 (AA'BB', *J* = 8.4 Hz, 4H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.15 (t, *J* = 6.7 Hz, 2H), 3.81 (s, 3H), 3.49 (s, 2H), 3.16 (t, *J* = 6.6 Hz, 2H), 2.24 (m, 2H), 2.13 (m, 2H), 1.56 (m, 4H), 1.34 (m, 2H) ppm.

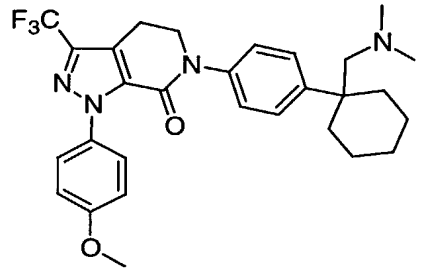
Part B. The product from part A (0.56 g, 1.12 mmol) was stirred in anhydrous CH_2Cl_2 (10 mL) at RT under N_2. NaOAc (0.37 g, 4.48 mmol, 4 eq) and molecular sieves (4Å, 1.0 g) were added followed by the addition of PCC (0.73 g, 3.36 mmol, 3 eq). The resulting slurry was stirred at RT for 1.5h. Analytical LC-MS showed completion of the reaction. The mixture was filtered, and rinsed with CH_2Cl_2. The filtrate was washed with H_2O (2x) and brine (2x), dried over Na_2SO_4, filtered, and concentrated to dryness to afford 1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclohexanecarbaldehyde (0.54 g, yield: 100%). LC/MS (ESI^+) 498.6 $(M+H)^+$, t_R = 3.20 min (10-90% CH_3CN in H_2O in a 4-min run).

Part C. The product from part B (0.4 g, 0.85 mmol) and methylamine hydrochloride (0.2 mg, 2.99 mmol, excess) were stirred in dichloroethane (8 mL) at RT under N_2. $NaBH(OAc)_3$ (0.85 mg, 4.01 mmol) was added followed by addition of HOAc (0.1 mL). The reaction mixture was stirred at RT for 2h. Analytical LC-MS showed completion of the reaction. The mixture was evaporated, and dissolved in aqueous MeOH. The mixture was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run) to afford 1-(4-methoxyphenyl)-6-(4-{1-

[(methylamino)methyl]cyclohexyl}phenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (120 mg. Yield: 29%). LC/MS (ESI$^+$) 513.4 $(M+H)^+$, t_R = 4.97 min. ^{1}H NMR (acetone-d_6) δ 7.52 (m, 4H), 7.38 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 4.19 (t, J = 6.3 Hz, 2H), 3.81 (s, 3H), 3.60 (s, 2H), 3.17 (t, J = 6.3 Hz, 2H), 2.62 (s, 6H), 2.16-1.64 (m, 8H) ppm.

Example 45

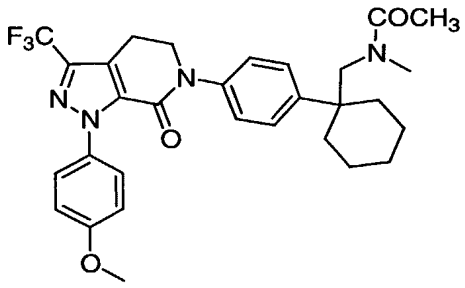
6-(4-{1-[(dimethylamino)methyl]cyclohexyl}phenyl)-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used for Example 44, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI$^+$) 526.4 $(M+H)^+$. ^{1}H NMR (acetone-d_6) δ 7.52 (m, 4H), 7.38 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 4.19 (t, J = 6.3 Hz, 2H), 3.81 (s, 3H), 3.60 (s, 2H), 3.17 (t, J = 6.3 Hz, 2H), 2.62 (s, 6H), 2.16-1.64 (m, 8H) ppm.

Example 46

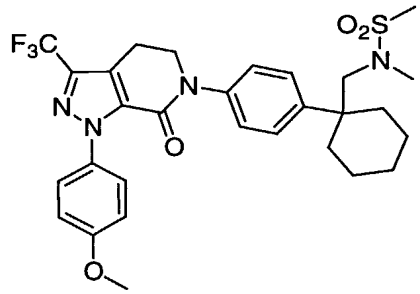
***N*-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclohexyl)methyl]-*N*-methylacetamide**



Following a procedure analogous to that used for Example 21, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 555.2 $(M+H)^+$, t_R = 6.76 min. ^1H NMR (acetone-d_6) δ 7.50 (d, J = 8.8 Hz, 2H), 7.38 (m, 4H), 6.98 (d, J = 9.2 Hz, 2H), 4.19 (t, J = 6.4 Hz, 2H), 3.83 (s, 3H), 3.39 (m, 2H), 3.17 (t, J = 6.4 Hz, 2H), 2.70, 2.42 (s, 3H), 2.02, 1.93 (m, 3H), 1.56 (m, 6H), 1.40 (m, 4H) ppm.

Example 47

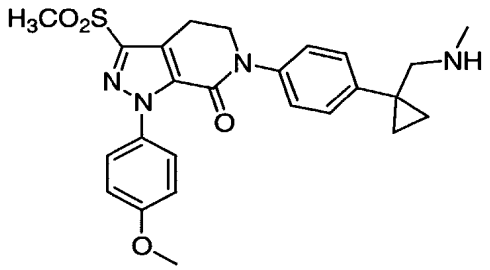
***N*-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclohexyl)methyl]-*N*-methylmethanesulfonamide**



Following a procedure analogous to that used for Example 23, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 591.2 $(M+H)^+$, t_R = 6.90 min. ^1H NMR (acetone-d_6) δ 7.50 (d, J = 8.8 Hz, 2H), 7.42 (AA'BB', J = 8.8 Hz, 4H), 6.98 (d, J = 8.7 Hz, 2H), 4.19 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.17 (t, J = 6.6 Hz, 2H), 3.10 (s, 2H), 2.69 (m, 3H), 2.21 (m, 3H), 1.57 (m, 6H), 1.29 (m, 4H) ppm.

Example 48

1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclopropyl}phenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro 7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Part A. 3-Chloro-5,6-dihydro-2(1*H*)-pyridinone (10.0 g, 38.17 mmol) and (1*Z*)-1-[chloro(methylsulfonyl)methylene]-2-(4-methoxyphenyl)hydrazine (5.0 g, 38.17 mmol) were stirred in toluene (200 mL) at RT under N_2. Et_3N (30 mL, 215.24 mmol) in toluene (150 mL) was added dropwise to the solution. After addition, the mixture was heated at 85°C overnight. After cooling, H_2O was added. It was extracted with EtOAc (2x). The organic layers were washed with H_2O (2x) and brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2, then CH_2Cl_2: EtOAc = 1:1, then EtOAc) to give 1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (3.85 g, yield: 31%). LC/MS (ESI$^+$) 322.4 $(M+H)^+$, t_R = 1.79 min (10-90% CH_3CN/H_2O in a 4-min run).

Part B. The product from part A (2.07 g, 6.23 mmol) and 4-iodophenylcyclopropylcarboxylic acid (2.75 g, 9.54 mmol, 1.5 eq) were stirred in DMSO (6 mL) under N_2. K_2CO_3 (2.57 g, 18.62 mmol, 3.0 eq) was added, followed by the addition of CuI (0.24 g, 20mol%) and 1,10-phenanthroline (0.23 g, 20 mol%). The resulting mixture was heated at 130°C overnight. After cooling, 1N HCl was added to acidify the solution. It was extracted with EtOAc (2x), washed with H_2O and

brine, dried over $MgSO_4$, filtered, and concentrated to dryness to give 1-{4-[1-(4-methoxyphenyl)-3-(methylsulfonyl)-7-oxo-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropanecarboxylic acid (2.95 g, yield: 95%). LC/MS (ESI^+) 482.4 $(M+H)^+$, t_R = 2.25 min (10-90% CH_3CN/H_2O in a 4-min run).

Part C. The product from part B (2.21 g, 4.59 mmol) was stirred in THF (15 mL) at 0°C under N_2. Et_3N (0.96 mL, 6.89 mmol, 1.5 eq) was added, followed by dropwise addition of $ClCO_2Et$ (0.57 mL, 5.48 mmol, 1.2 eq). The reaction mixture was then stirred at 0°C for 40 min. TLC showed completion of the reaction. The mixture was filtered, and rinsed with anhydrous THF. The THF filtrate (ca. 20 mL) was stirred at 0°C under N_2. MeOH (4 mL) was added, followed by portionwise addition of $NaBH_4$ (1.62 g, 42.63 mmol, 9 eq). The resulting mixture was stirred at 0°C for 35 min. Analytical LC-MS showed completion of the reaction. Sat'd Na_2SO_4 was then added. The mixture was extracted with EtOAc (2x). The organic layer was washed with H_2O (2x) and brine (2x), dried over Na_2SO_4, filtered, and concentrated to dryness to give 6-{4-[1-(hydroxymethyl)cyclopropyl]phenyl}-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (0.23 g, 84.7%). LC/MS (ESI^+) 468.4 $(M+H)^+$, t_R = 2.24 min (10-90% CH_3CN/H_2O in a 4-min run).

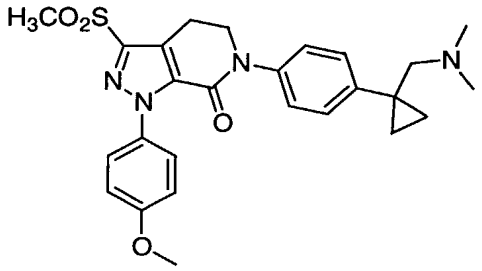
Part D. The product from part C (1.52 g, 3.27 mmol) was stirred in anhydrous CH_2Cl_2 (15 mL) at RT under N_2. NaOAc (0.54 g, 6.54 mmol, 2.0 eq) and molecular sieves (4Å, 1.5 g) were added, followed by the addition of PCC (1.06 g, 4.90 mmol, 1.5 eq). The resulting slurry was stirred at RT for 2 h. Analytical LC-MS showed completion of the reaction. The mixture was filtered through Celite®, and

rinsed with CH_2Cl_2. The filtrate was washed with H_2O (2x) and brine (2x), dried over Na_2SO_4, filtered, and concentrated to dryness to give 1-{4-[1-(4-methoxyphenyl)-3-(methylsulfonyl)-7-oxo-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropanecarbaldehyde (1.35 g, yield: 89%). LC/MS (ESI^+) 466.4 $(M+H)^+$, t_R = 2.38 min (10-90% CH_3CN/H_2O in a 4-min run).

Part E. The product from Part E (100 mg, 0.22 mmol) and methylamine hydrochloride (50 mg, excess) were stirred in dichloroethane (1 mL) in a capped vial. $NaBH(OAc)_3$ (250 mg, 1.16 mmol) was added followed by addition of one drop of HOAc. The reaction mixture was stirred at RT for 1.5 h. Analytical LC-MS showed completion of the reaction. The mixture was evaporated, and dissolved in aqueous MeOH. It was then purified by prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run) to obtain the product 1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclopropyl}phenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro 7*H*-pyrazolo[3,4-*c*]pyridin-7-one (33 mg, 31.3%). LC/MS (ESI^+) 481.4 $(M+H)^+$, t_R = 3.99 min. ^1H NMR (acetone-d_6) δ 7.53 (m, 4H), 7.32 (d, J = 7.7 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 4.13 (t, J = 6.4 Hz, 2H), 3.83 (s, 3H), 3.46 (m, 2H), 3.26 (m, 5H), 2.80 (m, 3H), 1.11 (m, 2H), 1.00 (m, 2H) ppm.

Example 49

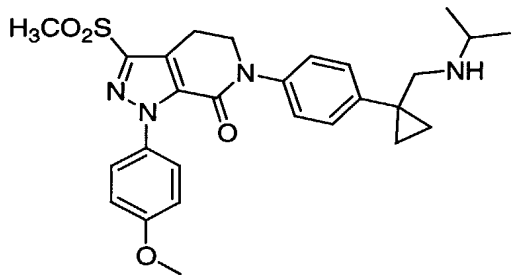
6-(4-{1-[(dimethylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used for the preparation of Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI$^+$) 495.6 $(M+H)^+$, t_R = 4.06 min. ^1H NMR (acetone-d_6) δ 7.55 (m, 4H), 7.38(d, J = 7.5 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 4.16 (d, J = 6.6 Hz, 2H), 3.86 (m, 3H), 3.71 (m, 2H), 3.64 (m, 2H), 3.29, 3.25 (m, 6H), 3.09 (t, J = 6.6 Hz, 2H), 2.99 (m, 3H), 1.17 (m, 2H), 1.13 (m, 2H) ppm.

Example 50

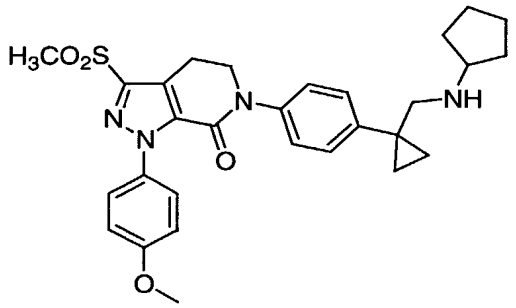
6-(4-{1-[(isopropylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used for the preparation of Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI$^+$) 509.6 $(M+H)^+$, t_R = 4.34 min. ^1H NMR (acetone-d_6) δ 7.58 (m, 4H), 7.33 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 9.1 Hz, 2H), 4.52 (m, 1H), 4.16 (d, J = 6.6 Hz, 2H), 3.86 (s, 3H), 3.79 (m, 2H), 3.61 (m, 1H), 3.48 (m, 2H), 3.29 (m, 5H), 1.33 (d, J = 6.2 Hz, 2H), 1.17 (m, 2H), 1.07 (m, 2H) ppm.

Example 51

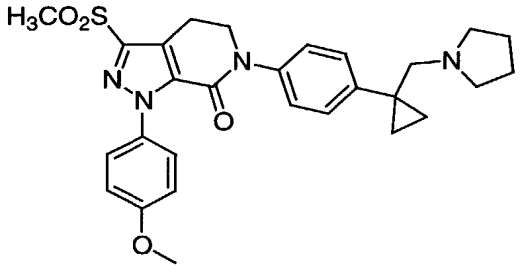
6-(4-{1-[(cyclopentylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt,



Following a procedure analogous to that used for the preparation of Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 535.4 $(M+H)^+$, t_R = 4.30 min. ^1H NMR (acetone-d_6) δ 7.55 (m, 4H), 7.33 (d, J = 7.4 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 4.16 (t, J = 6.6 Hz, 2H), 3.85 (s, 3H), 3.64 (m, 1H), 3.44 (m, 2H), 3.09 (m, 2H), 2.05 (m, 2H), 1.70 (m, 4H), 1.53 (m, 2H), 1.16 (m, 2H), 0.98 (m, 2H) ppm.

Example 52

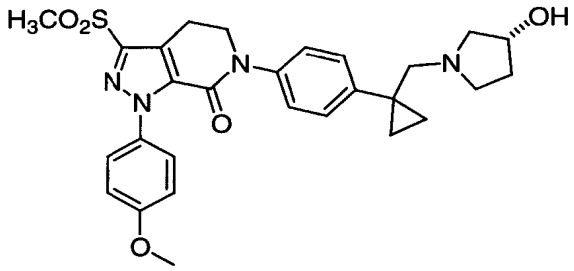
1-(4-methoxyphenyl)-3-(methylsulfonyl)-6-{4-[1-(1-pyrrolidinylmethyl)cyclopropyl]phenyl}-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used for the preparation of Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 521.4 $(M+H)^+$, t_R = 4.07 min. ^1H NMR (acetone-d_6) δ 7.58 (m, 4H), 7.37 (d, J = 7.7 Hz, 2H), 7.02 (d, J = 7.7 Hz, 2H), 4.19 (t, J = 6.6 Hz, 2H), 3.85 (s, 3H), 3.70 (m, 4H), 3.28 (m, 5H), 3.09 (t, J = 6.6 Hz, 2H), 2.08-2.03 (m, 2H), 1.16 (m, 2H), 1.06 (m, 2H) ppm.

Example 53

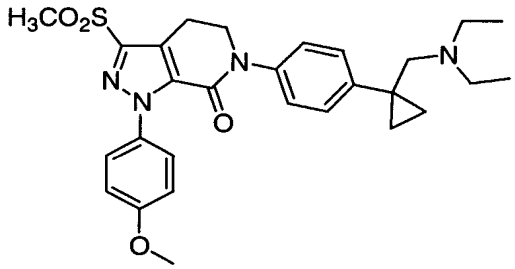
6-[4-(1-{[(3*R*)-3-hydroxy-1-pyrrolidinyl]methyl}cyclopropyl)phenyl]-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used for the preparation of Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 537.6 $(M+H)^+$, t_R = 3.90 min. ^1H NMR (acetone-d_6) δ 7.55 (m, 4H), 7.38 (m, 2H), 7.01 (d, J = 8.5 Hz, 2H), 4.52 (m, 1H), 4.17 (m, 2H), 3.85 (s, 3H), 3.79 (m, 2H), 3.63 (m, 2H), 3.29 (m, 5H), 3.09 (m, 2H), 2.17 (m, 2H), 1.17 (m, 2H), 1.07 (m, 2H) ppm.

Example 54

6-(4-{1-[(diethylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt

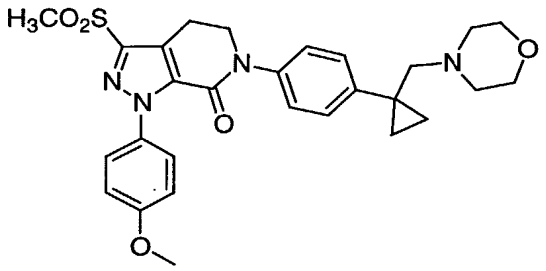


Following a procedure analogous to that used for the preparation of Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 523.4 $(M+H)^+$, t_R = 4.54 min.

^{1}H NMR (acetone-d_6) δ 7.55 (m, 4H), 7.35 (d, J = 7.5 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 4.16 (d, J = 6.6 Hz, 2H), 3.84 (s, 3H), 3.56 (m, 4H), 3.28 (m, 3H), 3.10 (m, 2H), 1.17 (m, 5H), 1.17 (m, 2H), 1.05 (m, 2H) ppm.

Example 55

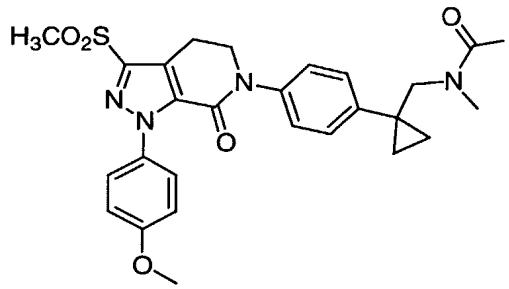
1-(4-methoxyphenyl)-3-(methylsulfonyl)-6-{4-[1-(4-morpholinylmethyl)cyclopropyl]phenyl}-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one



Following a procedure analogous to that used for the preparation of Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI$^+$) 537.6 $(M+H)^+$, t_R = 4.18 min. ^{1}H NMR (acetone-d_6) δ 7.54 (m, 4H), 7.36 (d, J = 7.7 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 4.17 (t, J = 6.6 Hz, 2H), 3.83 (m, 7H), 3.68 (m, 2H), 3.61 (m, 2H), 3.25 (m, 5H), 3.15 (m, 2H), 2.08-2.03 (m, 2H), 1.18 (m, 2H), 1.07 (m, 2H) ppm.

Example 56

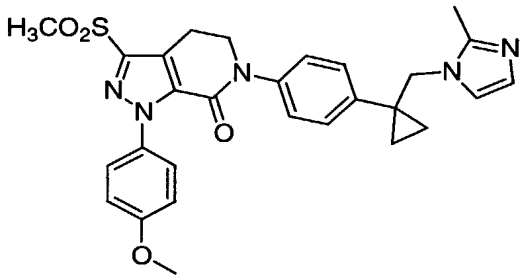
***N*-[(1-{4-[1-(4-methoxyphenyl)-3-(methylsulfonyl)-7-oxo-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropyl)methyl]-*N*-methylacetamide**



Following a procedure analogous to that used for the preparation of Example 21, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 523.6 $(M+H)^+$, t_R = 5.07 min.

Example 57

3-methanesulfonyl-1-(4-methoxyphenyl)-6-{4-[1-(2-methylimidazol-1-ylmethyl)cyclopropyl]phenyl}-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one



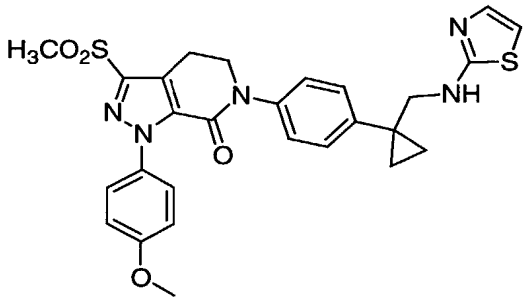
Part A. The product of part C in example 48 (0.69 g, 1.48 mmol) was stirred in CH_2Cl_2 (6 mL) at 0°C under N_2. PPh_3 (0.50 g, 1.91 mmol, 1.3 eq) was added, followed by the addition of CBr_4 (0.49 g, 1.48 mmol, 1.0 eq). The resulting mixture was stirred at 0°C for 30 min. LC-MS showed completion of the reaction (10-90% CH_3CN in H_2O in a 4-min run, t_R = 2.73 min). Sat'd NH4Cl was then added. The mixture was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated to dryness (0.39 g, yield: 50%). The product was used directly in the next step. LC/MS (ESI^+) 530.2, 532.2 $(M+H)^+$.

Part B. The product of Part A (0.13 g, 0.25 mmol), 2-methylimidazole (50 mg, 0.64 mmol), and K_2CO_3 (0.13 g, 1.0 mmol) were stirred in DMF (0.4 mL) under N_2. The mixture was heated at 85-90°C for 30 min. LC-MS showed completion of the reaction. After cooling to RT, H_2O was added. The mixture was purified by prep LC-MS (15-70% CH_3CN in H_2O) to

give pure 3-methanesulfonyl-1-(4-methoxyphenyl)-6-{4-[1-(2-methylimidazol-1-ylmethyl)cyclopropyl]phenyl}-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one (36 mg, yield %). LC/MS (ESI$^+$) 532.4 (M+H)$^+$, t_R = 4.43 min. ^{1}H NMR (acetone-d_6) δ 7.57 (m, 1H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.45 (m, 1H), 7.26 (AA'BB', *J* = 8.4 Hz, 4H), 6.99 (d, *J* = 9.1 Hz, 2H), 4.41 (s, 2H), 4.13 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 3H), 3.25 (m, 5H), 2.11 (s, 3H), 1.27 (t, *J* = 5.8 Hz, 2H), 1.03 (t, *J* = 5.8 Hz, 2H) ppm.

Example 58

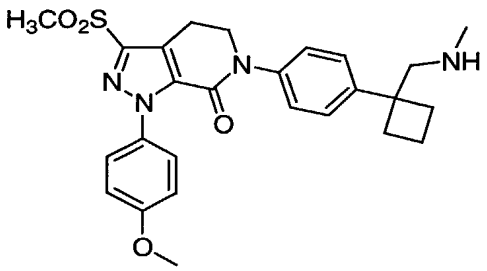
3-methanesulfonyl-1-(4-methoxyphenyl)-6-{4-[1-(thiazol-2-ylaminomethyl)cyclopropyl]phenyl}-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one



Following a procedure analogous to that of Example 25, the title compound was prepared. The product was purified by RP-prep LC-MS (35-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI$^+$) 550.4 (M+H)$^+$, t_R = 2.36 min.

Example 59

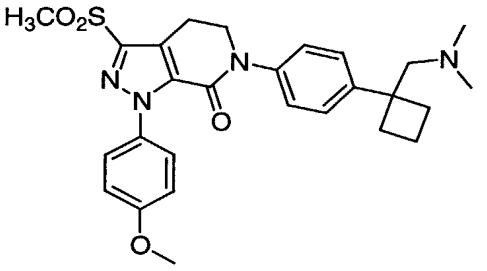
1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclobutyl}phenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro 7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used for Example 48, the title compound was prepared. It was then purified by prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run, t_R = 4.04 min). LC/MS (ESI^+) 495.4 $(M+H)^+$. ^1H NMR (acetone-d_6) δ 7.53 (d, J = 8.8 Hz, 4H), 7.32 (m, 4H), 7.00 (d, J = 9.1 Hz, 2H), 4.14 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.47 (br, s, 2H), 3.27 (m, 5H), 2.61 (br, s, 3H), 2.48-1.85 (m, 6H) ppm.

Example 60

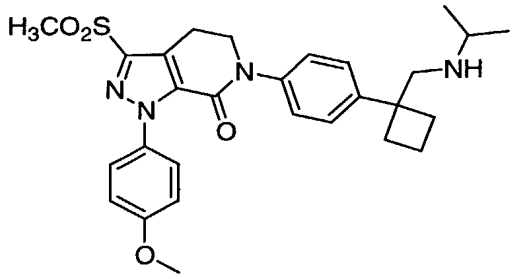
6-(4-{1-[(dimethylamino)methyl]cyclobutyl}phenyl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 509.4 $(M+H)^+$, t_R = 4.15 min.

Example 61

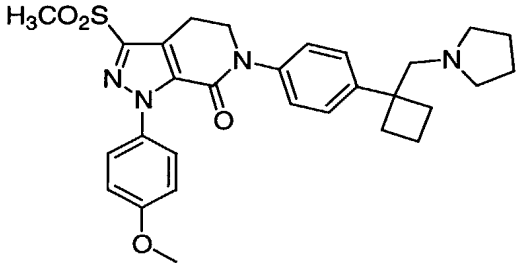
6-(4-{1-[(isopropylamino)methyl]cyclobutyl}phenyl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI$^+$) 523.4 $(M+H)^+$, t_R = 4.27 min. ^1H NMR (acetone-d_6) δ 7.53 (d, J = 9.1 Hz, 4H), 7.36 (AA'BB', J = 8.4 Hz, 4H), 7.00 (d, J = 8.8 Hz, 2H), 4.16 (t, J = 6.6 Hz, 2H), 3.84 (s, 3H), 3.52 (br, s, 2H), 3.27 (m, 5H), 2.81 (m, 1H), 2.42 (m, 4H), 2.04-1.94 (m, 2H), 1.17 (d, J = 7.3 Hz, 6H) ppm.

Example 62

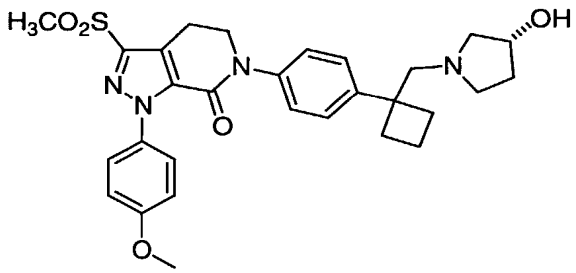
1-(4-methoxyphenyl)-3-(methylsulfonyl)-6-{4-[1-(1-pyrrolidinylmethyl)cyclobutyl]phenyl}-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (15-70% CH_3CN/H_2O in a 10-min run). LC/MS (ESI$^+$) 535.4 $(M+H)^+$, t_R = 4.74 min. ^1H NMR (acetone-d_6) δ 7.53 (d, J = 8.8 Hz, 2H), 7.41 (AA'BB', J = 8.8 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 4.18 (t, J = 6.6 Hz, 2H), 4.14 (m, 4H), 3.83 (m, 5H), 3.27 (m, 5H), 2.46 (m, 4H), 2.09-1.85 (m, 6H) ppm.

Example 63

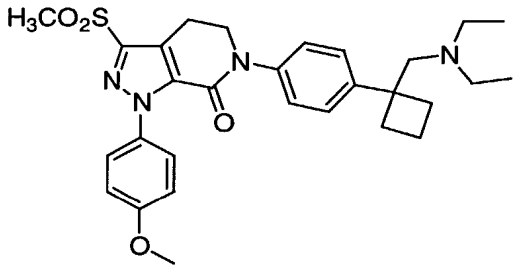
6-[4-(1-{[(3*R*)-3-hydroxy-1-pyrrolidinyl]methyl}cyclobutyl)phenyl]-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI$^+$) 551.4 $(M+H)^+$, t_R = 4.06 min. ^{1}H NMR (acetone-d_6) δ 7.53 (d, J = 9.1 Hz, 2H), 7.40 (m, 4H), 6.99 (d, J = 9.1 Hz, 2H), 4.30 (m, 1H), 4.18 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.78 (m, 2H), 3.49 (m, 2H), 3.27 (m, 5H), 2.82 (m, 2H), 2.46 (m, 6H), 2.10-1.81 (m, 2H) ppm.

Example 64

6-(4-{1-[(diethylamino)methyl]cyclobutyl}phenyl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt

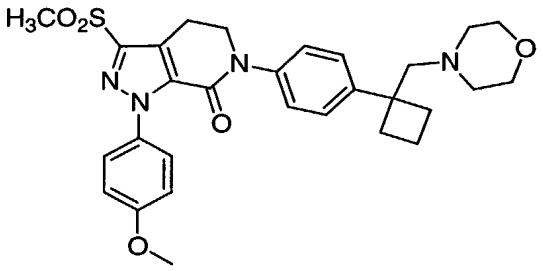


Following a procedure analogous to that used in Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI$^+$) 537.4 $(M+H)^+$, t_R = 4.62 min. ^{1}H NMR (acetone-d_6) δ 7.53 (d, J = 8.8 Hz, 4H), 7.41 (d, J = 8.4 Hz, 2H), 7.00

(d, J = 9.2 Hz, 2H), 4.18 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.74 (m, 2H), 3.27 (s+t, 5H), 3.03 (m, 4H), 2.49 (t, J = 7.5 Hz, 4H), 2.09-1.89 (m, 2H), 1.19 (t, J = 7.4 Hz, 6H) ppm.

Example 65

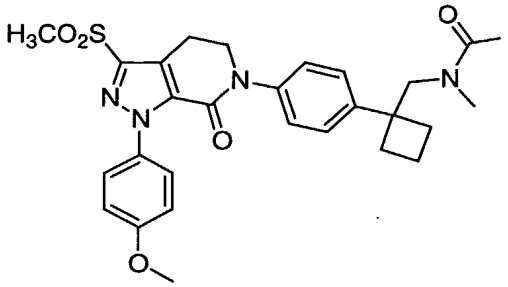
1-(4-methoxyphenyl)-3-(methylsulfonyl)-6-{4-[1-(4-morpholinylmethyl)cyclobutyl]phenyl}-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 551.4 $(M+H)^+$, t_R = 4.12 min. ^1H NMR (acetone-d_6) δ 7.53 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 9.1 Hz, 2H), 4.17 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.74 (m, 10H), 3.27 (m, 5H), 2.46 (m, 4H), 2.10-1.84 (m, 2H) ppm.

Example 66

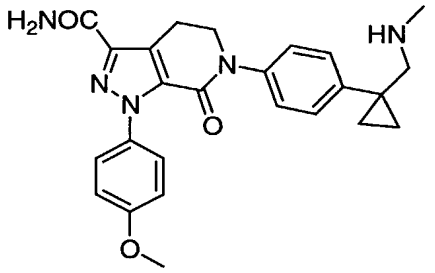
***N*-[(1-{4-[1-(4-methoxyphenyl)-3-(methylsulfonyl)-7-oxo-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropyl)methyl]-*N*-methylacetamide**



Following a procedure analogous to that of Example 21, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). ESI, LC/MS (ESI^+) 551.4 $(M+H)^+$, t_R = 4.12 min.

Example 67

1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclopropyl}phenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide, trifluoroacetic acid salt



Part A. 4-Iodophenylcyclopropyl acetic acid (1.93 g, 6.70 mmol) and 1-(4-methoxyphenyl)-3-(ethoxycarbonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (1.41 g, 4.46 mmol) were stirred in DMSO (4 mL) under N_2. K_2CO_3 (1.84 g, 13.33 mmol, 3.0 eq) was added followed by the addition of 1,10-phenanthroline (0.15 g, 20 mol%) and CuI (0.16 g, 20mol%). The resulting mixture was stirred at 110°C overnight. LC-MS showed completion of the reaction. EtOAc was added to the cooled solution. It was acidified with 1N HCl, and the organic layer was washed with H_2O, and brine, dried over $MgSO_4$, filtered, and concentrated to afford 1-{4-[3-(ethoxycarbonyl)-1-(4-methoxyphenyl)-7-oxo-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropanecarboxylic acid (1.54 g, yield: 72.6%). LC/MS (ESI^+) 476.4 $(M+H)^+$, t_R = 2.58 min (10-90% CH_3CN/H_2O in a 4-min run).

Part B. The product from part B (1.43 g, 3.01 mmol) was stirred in THF (13 mL) at 0°C under N_2. Et_3N (0.63 mL, 4.32

mmol, 1.5 eq) was added followed by dropwise addition of ClCOOEt (0.37 mL, 4.16 mmol, 1.3 eq). The reaction mixture was then stirred at 0°C for 20 min. TLC showed completion of the reaction. The mixture was filtered, and rinsed with anhydrous THF. The THF filtrate (ca. 20 mL) was stirred at 0°C under N_2. MeOH (3 mL) was added followed by the addition of $NaBH_4$ (1.03 g, 27.10 mmol, 10 eq). The resulting mixture was stirred at 0°C for 15 min. Analytical LC-MS showed completion of the reaction. Sat'd Na_2SO_4 was then added. The mixture was extracted with EtOAc (2x). The organic layer was washed with H_2O (2x) and brine (2x), dried over Na_2SO_4, filtered, and concentrated to dryness to give 6-{4-[1-(hydroxymethyl)cyclopropyl]phenyl}-1-(4-methoxyphenyl)-3-(ethoxycarbonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (1.30 g, 99%). LC/MS (ESI^+) 462.6 $(M+H)^+$, t_R = 2.57 min (10-90% CH_3CN/H_2O in a 4-min run).

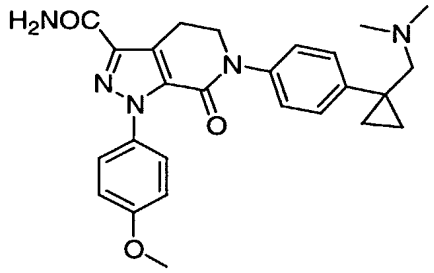
Part C. The product from part B (1.90 g, 4.12 mmol) was stirred in anhydrous CH_2Cl_2 (13 mL) at RT under N_2. NaOAc (1.01 g, 12.20 mmol, 3 eq) and molecular sieves (2.0 g) were added followed by the addition of PCC (1.78 g, 8.24 mmol, 2 eq). The resulting slurry was stirred at RT for 1.5 h. Analytical LC-MS showed completion of the reaction. The mixture was filtered, and rinsed with CH_2Cl_2. The filtrate was washed with H_2O (2x) and brine (2x), dried over Na_2SO_4, filtered, and concentrated to dryness to afford ethyl 6-[4-(1-formylcyclopropyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylate (1.90 g, yield: 100%). LC/MS (ESI^+) 460.6 $(M+H)^+$, t_R = 2.69 min (10-90% CH_3CN/H_2O in a 4-min run).

Part D. The product from part C (250 mg, 0.55 mmol), methylamine hydrochloride (0.5 g, excess) were stirred in dichloroethane (15 mL) at RT under N_2. $NaBH(OAc)_3$ (1.03 g, 4.86 mmol) was added followed by addition of three drops of HOAc. The reaction mixture was stirred at RT for 1.5 h. Analytical LC-MS showed completion of the reaction. The mixture was quenched with H_2O, and extracted with EtOAc (2x). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness to obtain crude ethyl 1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclopropyl}phenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylate (109 mg, yield: 42%). LC/MS (ESI^+) 475.4 $(M+H)^+$, t_R = 2.08 min.

Part E. The product from part D (50 mg, 0.105 mmol) was stirred in ethylene glycol (saturated with NH_3) in a capped Pyrex tube at 80°C for 4 h. After cooling, the mixture was diluted with MeOH, and purified by prep LC-MS (5-98% CH_3CN in H_2O in a 10-min run) to afford 1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclopropyl}phenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide (29 mg, yield: 60%). LC/MS (ESI^+) 445.4 $(M+H)^+$, t_R = 3.53 min. ^1H NMR (acetone-d_6) δ 7.49 (m, 4H), 7.29 (d, J = 8.1 Hz, 2H), 6.97 (d, J = 9.1 Hz, 2H), 4.06 (t, J = 6.6 Hz, 2H), 3.82 (s, 3H), 3.32 (s, 2H), 3.24 (t, J = 6.6 Hz, 2H), 2.66 (s, 3H), 1.10 (m, 2H), 0.94 (m, 2H) ppm.

Example 68

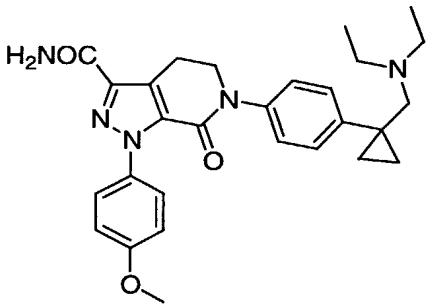
6-(4-{1-[(dimethylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 67, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI$^+$) 460.6 $(M+H)^+$, t_R = 3.93 min. ^1H NMR (acetone-d_6) δ 7.52 (m, 4H), 7.33 (m, 2H), 6.97 (d, J = 9.2 Hz, 2H), 4.10 (t, J = 6.3 Hz, 2H), 3.82 (s, 3H), 3.52 (m, 2H), 3.26 (t, J = 6.3 Hz, 2H), 2.69 (m, 6H), 1.18 (m, 2H), 1.04 (m, 2H) ppm.

Example 69

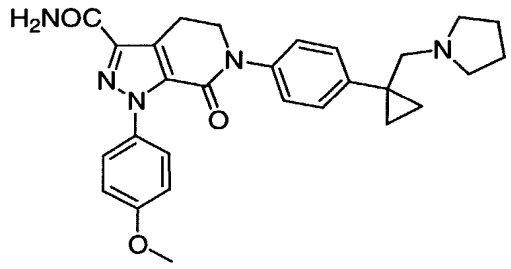
6-(4-{1-[(diethylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 67, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI$^+$) 488.6 $(M+H)^+$, t_R = 3.90 min. ^1H NMR (acetone-d_6) δ 7.57 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 9.1 Hz, 2H), 4.08 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.62 (m, 2H), 3.24 (m, 6H), 1.16 (m, 8H), 1.05 (m, 2H) ppm.

Example 70

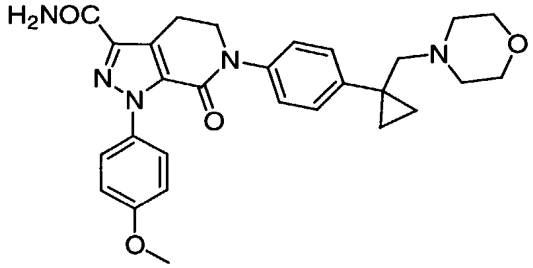
1-(4-methoxyphenyl)-7-oxo-6-{4-[1-(1-pyrrolidinylmethyl)cyclopropyl]phenyl}-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 67, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI$^+$) 486.4 $(M+H)^+$, t_R = 3.88 min. ^{1}H NMR (acetone-d_6) δ 7.52 (m, 2H), 7.32 (m, 4H), 6.99 (m, 2H), 4.09 (m, 2H), 3.82 (s, 3H), 3.56 (m, 6H), 3.26 (m, 2H), 1.91 (m, 4H), 1.13 (m, 2H), 0.98 (m, 2H) ppm.

Example 71

1-(4-methoxyphenyl)-6-{4-[1-(4-morpholinylmethyl)cyclopropyl]phenyl}-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide, trifluoroacetic acid salt

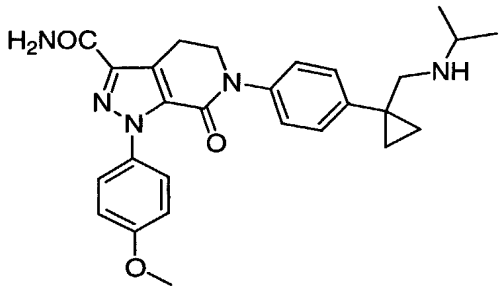


Following a procedure analogous to that used in Example 67, the title compound was prepared. It was then purified by prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run, t_R = 3.67 min). LC/MS (ESI$^+$) 502.6 $(M+H)^+$. ^{1}H NMR (acetone-d_6) δ 7.51 (d, J = 8.6 Hz, 4H), 7.34 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4

Hz, 4H), 6.95 (d, J = 9.2 Hz, 2H), 4.09 (t, J = 6.6 Hz, 2H), 3.82 (s, 3H), 3.48 (m, 6H), 3.26 (t, J = 6.6 Hz, 2H), 2.82 (m, 2H), 2.40 (m, 2H), 0.81 (m, 2H), 0.73 (m, 2H) ppm.

Example 72

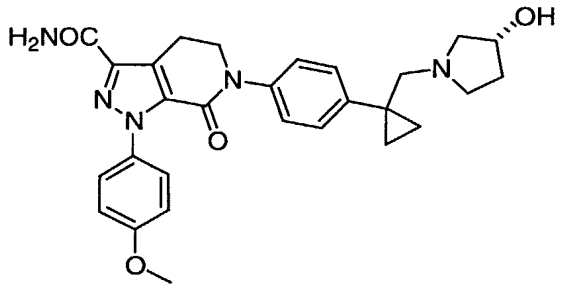
6-(4-{1-[(isopropylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 67, the title compound was prepared. It was then purified by prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run, t_R = 4.18 min). LC/MS (ESI$^+$) 474.4 $(M+H)^+$. ^1H NMR (acetone-d_6) δ 7.53 (m, 4H), 7.28 (d, J = 8.1 Hz, 2H), 6.97 (d, J = 7.7 Hz, 2H), 4.08 (m, 2H), 3.82 (s, 3H), 3.35 (m, 3H), 3.25 (m, 2H), 1.27 (d, J = 6.2 Hz, 6H), 1.11 (m, 2H), 0.92 (m, 2H) ppm.

Example 73

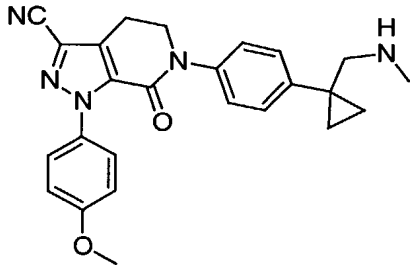
6-[4-(1-{[(3*R*)-3-hydroxy-1-pyrrolidinyl]methyl}cyclopropyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 67, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 502.4 $(M+H)^+$, t_R = 3.81 min.

Example 74

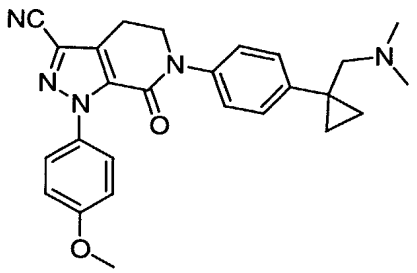
1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclopropyl}phenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile, trifluoroacetic acid salt



The product of Example 67 (15 mg) was stirred in DMF (0.5 mL) at RT in a capped vial. Two drops of thionyl chloride was added. The reaction was completed in 10 min. The mixture was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run) to give pure 1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclopropyl}phenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile (11 mg, yield: 76.2%). LC/MS (ESI^+) 428.4 $(M+H)^+$, t_R = 4.49 min.

Example 75

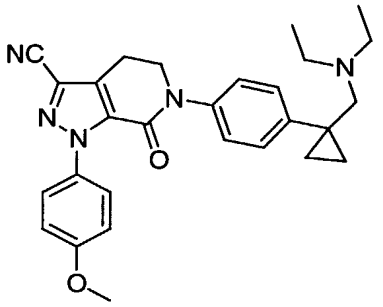
6-(4-{1-[(dimethylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 74, the title compound was prepared. It was then purified by prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run, t_R = 4.44 min). LC/MS (ESI^+) 442.6 $(M+H)^+$. ^1H NMR (acetone-d_6) δ 7.53 (m, 4H), 7.33 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 9.2 Hz, 2H), 4.18 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.57 (s, 2H), 3.18 (t, J = 6.6 Hz, 2H), 2.78 (s, 6H), 1.16 (m, 2H), 1.06 (m, 2H) ppm.

Example 76

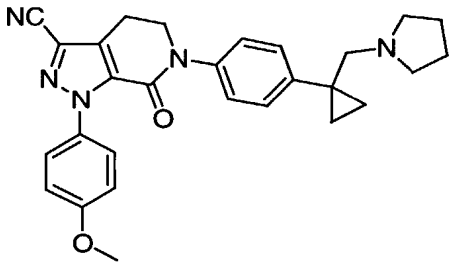
6-(4-{1-[(diethylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 74, the title compound was prepared. It was then purified by prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run, t_R = 4.60 min). LC/MS (ESI^+) 470.6 $(M+H)^+$. ^1H NMR (acetone-d_6) δ 7.58 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 9.1 Hz, 2H), 4.19 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.58-3.18 (m, 6H), 3.19 (t, J = 6.6 Hz, 2H), 1.18 (m, 8H), 1.06 (m, 2H) ppm.

Example 77

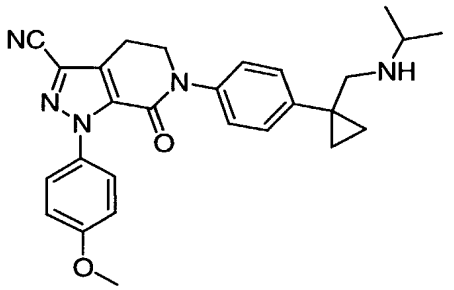
1-(4-methoxyphenyl)-7-oxo-6-{4-[1-(1-pyrrolidinylmethyl)cyclopropyl]phenyl}-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile, trifluoroacetic acid salt



Following a procedure analogous to that used in step F of Example 74, the title compound was prepared. LC/MS (ESI$^+$) 468.4 (M+H)$^+$, t_R = 4.49 min. ^{1}H NMR (acetone-d_6) δ 7.52 (d, J = 9.0 Hz, 2H), 7.44 (AA'BB', J = 8.6 Hz, 4H), 6.99 (d, J = 8.8 Hz, 2H), 4.18 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.59 (m, 2H), 3.19 (t, J = 6.6 Hz, 2H), 2.75 (m, 4H), 2.01 (m, 4H), 1.14 (m, 2H), 1.00 (m, 2H).

Example 78

6-(4-{1-[(isopropylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile, trifluoroacetic acid salt

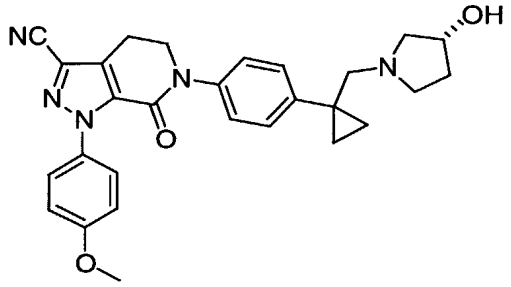


Following a procedure analogous to that used in Example 74, the title compound was prepared. It was then purified by prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run, t_R = 4.57 min). LC/MS (ESI$^+$) 456.6 (M+H)$^+$. ^{1}H NMR (acetone-d_6) δ 7.53 (m, 4H), 7.31 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 9.1 Hz, 2H),

4.17 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.19 (t, J = 6.6 Hz, 2H), 3.17 (m, 3H), 1.28 (d, J = 6.6 Hz, 6H), 1.13 (m, 2H), 0.93 (m, 2H) ppm.

Example 79

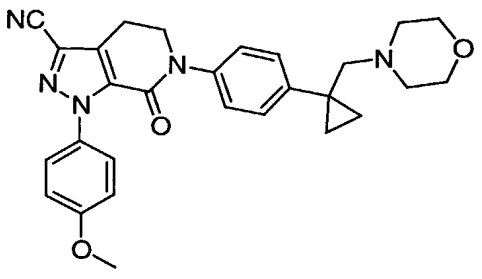
6-[4-(1-{[(3*R*)-3-hydroxy-1-pyrrolidinyl]methyl}cyclopropyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 74, the title compound was prepared. It was then purified by prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run, t_R = 4.34 min). LC/MS (ESI$^+$) 484.4 $(M+H)^+$. ^1H NMR (acetone-d_6) δ 7.53 (m, 4H), 7.35 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 9.2 Hz, 2H), 4.19 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.62 (m, 5H), 3.19 (t, J = 6.6 Hz, 2H), 2.91 (m, 2H), 1.85 (m, 2H), 1.18 (m, 2H), 1.01 (m, 2H) ppm.

Example 80

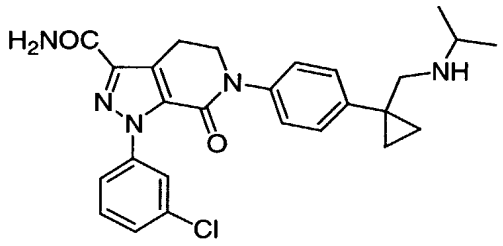
1-(4-methoxyphenyl)-6-{4-[1-(4-morpholinylmethyl)cyclopropyl]phenyl}-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 67, the title compound was prepared. It was then purified by prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run, t_R = 4.46 min). LC/MS (ESI^+) 484.6 $(M+H)^+$. ^1H NMR (acetone-d_6) δ 7.52 (m, 4H), 7.32 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 9.2 Hz, 2H), 4.17 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.47 (m, 7H), 3.62 (s, 2H), 3.49 (m, 2H), 3.17 (t, J = 6.6 Hz, 2H), 3.07 (m, 2H), 1.17 (m, 2H), 1.06 (m, 2H) ppm.

Example 81

1-(3-chlorophenyl)-6-{4-[1-(isopropylamino)methyl)cyclopropyl]phenyl}-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide



Part A. 1-(3-Chlorophenyl)-3-(ethoxycarbonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (1.14 g, 3.57 mmol) and 4-iodophenylcyclopropyl acetic acid (1.13 g, 1.1 eq) were stirred in DMSO (4 mL) under N_2. K_2CO_3 (1.48 g, mmol, 3 eq) was added, followed by the addition of 1,10-phenanthroline (0.13 g, 20 mol%) and CuI (0.14 g, 20 mol%). The resulting mixture was stirred at 130°C overnight. LC-MS showed completion of the reaction. EtOAc was added to the cooled solution. It was washed with 1N HCl, H_2O, and brine; dried over $MgSO_4$; filtered; and concentrated in *vacuo* to give almost pure 1-{4-[1-(3-chlorophenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropanecarboxylic acid (0.87 g, yield: 51%). LC/MS (ESI^+) 480.4 $(M+H)^+$.

Part B. The product from Part A (0.54 g, 1.13 mmol) was stirred in THF (6 mL) at 0°C under N_2. Et_3N (0.24 mL, 1.5 eq) was added, followed by dropwise addition of ClCOOEt (0.14 mL, 1.3 eq). The reaction mixture was then stirred at 0°C for 1 h. TLC showed the completion of the reaction. The mixture was filtered through a filter funnel and rinsed with anhydrous THF. The THF filtrate (ca. 10 mL) was stirred at 0°C under N_2. $NaBH_4$ (0.52 g, 10 eq) was added, followed by the addition of MeOH (2.5 mL). The resulting mixture was stirred at 0°C. Analytical LC-MS showed completion of the reaction. Sat'd Na_2SO_4 was then added. The mixture was extracted with EtOAc (2x). The organic layer was washed with H_2O (2x) and brine (2x), dried over Na_2SO_4, filtered, and concentrated to dryness to give 1-(3-chlorophenyl)-6-{4-[1-(hydroxymethyl)cyclopropyl]phenyl}-3-(ethoxycarbonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (0.31 g, yield: 52.4%). LC/MS (ESI^+) 466.4 $(M+H)^+$.

Part C. The product from Part B (0.31 g, 0.22 mmol) was stirred in anhydrous CH_2Cl_2 (5 mL) at RT under N_2. NaOAc (0.16 g, 1.95 mmol) and molecular sieves (0.5 g) were added, followed by the addition of PCC (0.29 g, 1.34 mmol). The resulting slurry was stirred at RT for 1.5h. Analytical LC-MS showed completion of the reaction. The mixture was filtered through Celite, and rinsed with CH_2Cl_2. The filtrate was washed with H_2O (2x), brine (2x), dried over Na_2SO_4, filtered, and concentrated to dryness to give almost pure 1-(3-chlorophenyl)-6-[4-(1-(formylcyclopropyl)phenyl]-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid ethyl ester (0.20 g, yield: 87.4%). LC/MS (ESI^+) 464.4 $(M+H)^+$.

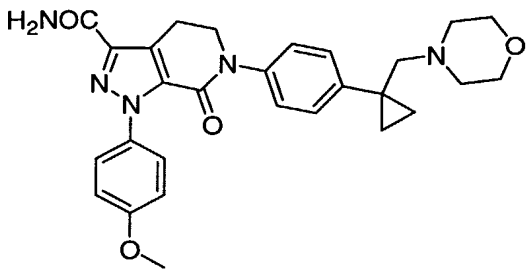
Part D. The product from Part C (100 mg) and isopropyl amine (0.1 mL, excess) were stirred in dichloroethane (1

mL) in a capped vial. $NaBH(OAc)_3$ (200 mg) was added, followed by addition of one drop of HOAc. The reaction mixture was stirred at RT for 1.5 h. Analytical LC-MS showed completion of the reaction. The mixture was evaporated, and dissolved in aqueous MeOH. It was then purified by prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run) to obtain pure 1-(3-chlorophenyl)-6-{4-[1-(isopropylamino)methyl)cyclopropyl]phenyl}-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide (60 mg, yield: 55%). LC/MS (ESI^+) 507.4 $(M+H)^+$, t_R = 4.68 min.

Part E. The product from part D (60 mg) was stirred in ethylene glycol (saturated with NH_3) in a capped Pyrex tube at 80°C for 4 h. After cooling, the mixture was diluted with MeOH and purified by prep LC-MS (5-98% CH_3CN in H_2O in a 10-min run) to afford the title compound (35 mg, yield: 62%). LC/MS (ESI^+) 478.4 $(M+H)^+$, t_R = 4.34 min. ^1H NMR (acetone-d_6) δ 7.74 (s, 1H), 7.63 (m, 1H), 7.45 (m, 4H), 7.30 (d, J = 8.4 Hz, 2H), 4.11 (t, J = 6.6 Hz, 2H), 3.44 (m, 1H), 3.38 (m, 2H), 3.26 (t, J = 6.6 Hz, 2H), 1.29 (d, J = 6.6 Hz, 6H), 1.12 (m, 2H), 0.94 (m, 2H) ppm.

Example 82

1-(3-chlorophenyl)-6-{4-[1-(4-morpholinylmethyl)cyclopropyl]phenyl}-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide, trifluoroacetic acid salt

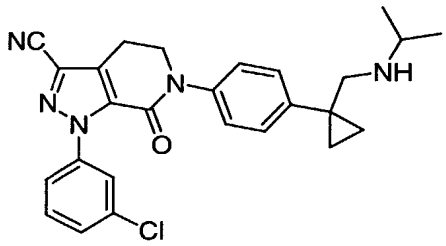


Following a procedure analogous to that used in Example 81, the title compound was prepared. The product was purified

by prep LC-MS (5-98% CH_3CN in H_2O in a 10-min run). LC/MS (ESI^+) 506.6 $(M+H)^+$, t_R = 4.57 min. ^1H NMR (acetone-d_6) δ 7.73 (s, 1H), 7.63 (m, 1H), 7.47 (m, 4H), 7.29 (m, 2H), 4.09 (t, J = 6.6 Hz, 2H), 3.74 (m, 4H), 3.53 (m, 2H), 3.27 (m, 2H), 3.07 (m, 4H), 1.07 (m, 2H), 1.00 (m, 2H) ppm.

Example 83

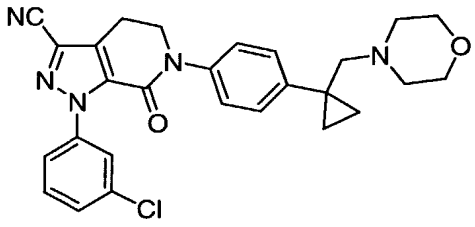
6-(4-{1-[(isopropylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile, trifluoroacetic acid salt



Following a procedure analogous to that used in step F of Example 74, the title compound was prepared. It was then purified by prep LC-MS (35-98% CH_3CN/H_2O in a 10-min run, t_R = 2.78 min). LC/MS (ESI^+) 460.6 $(M+H)^+$. ^1H NMR (acetone-d_6) δ 7.75 (s, 1H), 7.63 (m, 1H), 7.53 (m, 4H), 7.31 (d, J = 8.8 Hz, 2H), 4.19 (t, J = 6.6 Hz, 2H), 3.48 (m, 1H), 3.41 (m, 2H), 3.21 (t, J = 6.6 Hz, 2H), 1.29 (d, , J = 6.3 Hz, 6H), 1.14 (m, 2H), 0.95 (m, 2H) ppm.

Example 84

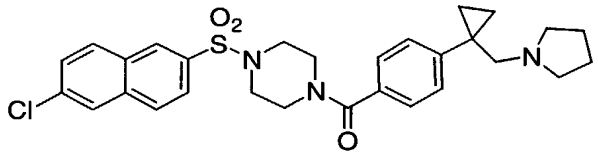
1-(4-methoxyphenyl)-6-{4-[1-(4-morpholinylmethyl)cyclopropyl]phenyl}-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 74, the title compound was prepared. It was then purified by prep LC-MS (35-98% CH_3CN/H_2O in a 10-min run, t_R = 2.80 min). LC/MS (ESI^+) 488.6 $(M+H)^+$. ^1H NMR (acetone-d_6) δ 7.73 (s, 1H), 7.62 (m, 1H), 7.54 (m, 4H), 7.34 (m, 2H), 4.19 (m, 2H), 3.83 (m, 8H), 3.61 (m, 2H), 3.19 (m, 2H), 1.17 (m, 2H), 1.05 (m, 2H) ppm.

Example 85

1-[(6-chloro-2-naphthyl)sulfonyl]-4-{4-[1-(1-pyrrolidinylmethyl)cyclopropyl]benzoyl}piperazine



Part A. 1-(4-Iodophenyl)cyclopropane carboxylic acid (0.64 g, 2.25 mmol) was stirred in THF (10 mL) at 0°C under N_2. Et_3N (0.47 mL, 3.37 mmol) was added, followed by dropwise addition of $ClCO_2Et$ (0.28 mL, 2.93 mmol). The reaction mixture was then stirred at 0°C for 30 min. TLC showed the completion of the reaction. The mixture was filtered through a filter funnel and rinsed with anhydrous THF. The THF filtrate (ca.15 mL) was stirred at 0°C under N_2. $NaBH_4$ (0.41 g, 10.8 mmol) was added, followed by addition of MeOH (3 mL). The resulting mixture was stirred at 0°C for 30 min. Analytical LC-MS showed completion of the reaction. Sat'd Na_2SO_4 was then added. The mixture was extracted with EtOAc (2x). The organic layer was washed with H_2O (2x) and brine (2x), dried over Na_2SO_4, filtered, and concentrated to dryness. The resulting alcohol was stirred in anhydrous CH_2Cl_2 (10 mL) at RT under N_2. NaOAc (0.42 g, 5.12 mmol) and molecular sieves (4Å, 0.75 g) were added, followed by the addition of PCC (0.83 g, 3.84 mmol). The resulting slurry was stirred at RT for 1.5 h. Analytical LC-MS showed completion of the reaction. The mixture was

filtered through Celite, and rinsed with CH_2Cl_2. The filtrate was washed with H_2O (2x) and brine (2x), dried over Na_2SO_4, filtered, and concentrated in vacuo to give almost pure 4-iodophenylcyclopropanecarbaldehyde. This aldehyde and pyrrolidine (0.37 mmol) were stirred in dichloroethane (6 mL) at RT under N_2. $NaBH(OAc)_3$ (1.37 mg, mmol) was added, followed by addition of several drops of HOAc. The reaction mixture was stirred at RT for 20 min. Analytical LC-MS showed completion of the reaction. H_2O was added. The mixture was extracted with EtOAc; and the organic extracts were washed with H_2O (2x) and brine (2x), dried over Na_2SO_4, filtered, and concentrated to dryness to give almost pure 1-{[1-(4-iodophenyl)cyclopropyl]methyl}pyrrolidine (0.41 g, yield % for 3 steps). LC/MS (ESI^+) 328.2 $(M+H)^+$ (10-90% CH_3CN/H_2O in a 4-min run, t_R = 1.77 min).

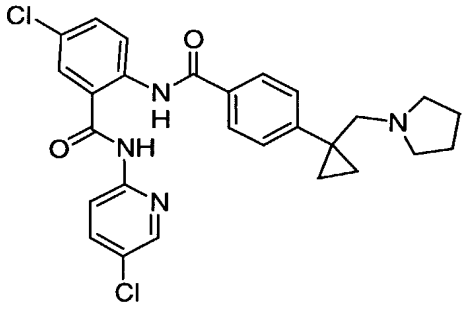
Part B. The product from part A (0.40 g, 1.24 mmol), KOAc (0.61 g, 5.0 eq), $Pd(OAc)_2$ (0.03 g, 0.1 eq), and dppf (0.14 g, 0.2 eq) were stirred in DMF (3 mL) at RT. The mixture was degassed twice and purged with CO. The mixture was heated at 60°C under CO atmosphere with a balloon for 2.5 h. LS-MS showed completion of the reaction. After cooling, H_2O was added. The mixture was extracted with EtOAc (2x). The aqueous layer was then acidified, and concentrated to dryness. MeOH was added, and filtered off inorganic salts. The filtrate was concentrated and vacuum dried to give almost pure 4-[1-(1-pyrrolidinylmethyl)cyclopropyl]benzoic acid (0.32 g, yield: 96%). LC/MS (ESI^+) 246.4 $(M+H)^+$ (10-90% CH_3CN/H_2O in a 4-min run, t_R = 1.32 min).

Part C. The product of part B (0.41 g, 1.68 mmol) was stirred in CH_2Cl_2 (10 mL) at RT under N_2. $(COCl)_2$ (0.5 mL)

was added, followed by the addition of one drop of DMF. The mixture was stirred at RT for 1 h. The solvent was evaporated and dried in *vacuo*. The resulting acid chloride (0.16 g, 0.61 mmol) was dissolved in CH_2Cl_2 (10 mL), 1-[(6-chloro-2-naphthyl)sulfonyl]piperazine (0.21 g, 0.61 mmol) was added, followed by the addition of DIEA (0.21 mL, 1.21 mmol). The resulting mixture was stirred at RT for 20 min. Analytical LC-MS showed completion of the reaction. The solvent was evaporated. The residue was dissolve in MeOH, and purified by RP Prep LC-MS (5-98% CH_3CN in H_2O in a 10-min run) to give pure title compound (210 mg, yield: 64.1%). It was then purified by prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run, t_R = 4.71 min). LC/MS (ESI^+) 538.4 $(M+H)^+$.

Example 86

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-({4-[1-(1-pyrrolidinylmethyl)cyclopropyl]benzoyl}amino)benzamide, trifluoroacetic acid salt



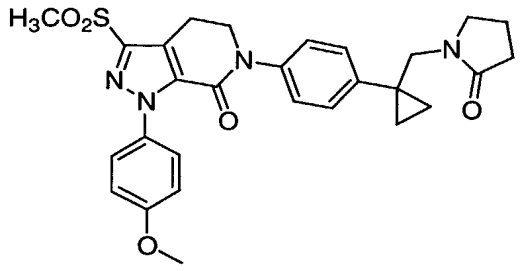
Part A. The product from Part B of Example 85 (0.16 g, 0.65 mmol) was stirred in CH_2Cl_2 (5 mL) at RT under N_2. $(COCl)_2$ (0.2 mL) was added. The mixture was stirred at RT for 1 h. The solvent was evaporated and dried in *vacuo*. The resulting acid chloride was dissolved in CH_2Cl_2 (6 mL), 2-amino-5-chlorobenzoic acid methyl ester (0.16 g, 0.86 mmol) was added, followed by the addition of DIEA (0.30 mL). The resulting mixture was stirred at RT for 2 h. Analytical LC-MS showed completion of the reaction. The solvent was evaporated. The residue was dissolve in EtOAc,

washed with H_2O, brine, dried over $MgSO_4$, and concentrated to give methyl 5-chloro-2-({4-[1-(1-pyrrolidinylmethyl)cyclopropyl]benzoyl}amino)benzoate (55 mg, yield: 21%). LC/MS (ESI^+) 413.4 $(M+H)^+$, t_R = 2.19 min (10-90% CH_3CN/H_2O in a 4-min run).

Part B. The product from Part A (30 mg) and 5-chloro-2-aminopyridine (14 mg) were stirred in CH_2Cl_2 (1 mL) at RT under N_2. Me_3Al in toluene (0.45 mL, 0.23 mmol) was added dropwise. The resulting solution was stirred at RT for 1h and at reflux for 2h. The solvent was evaporated after cooling. The residue was dissolved in MeOH, and purified by LC-MS (5-98% CH_3CN in H_2O in a 10-min run) to give pure 5-chloro-*N*-(5-chloro-2-pyridinyl)-2-({4-[1-(1-pyrrolidinylmethyl)cyclopropyl]benzoyl}amino)benzamide (6 mg, yield: 16%). LC/MS (ESI^+) 509.2 $(M+H)^+$, t_R = 2.21 min (10-90% CH_3CN/H_2O in a 4-min run).

Example 87

1-(4-Methoxyphenyl)-3-methanesulfonyl-6-{4-[1-(2-oxo-pyrrolidin-1-ylmethyl)cyclopropyl]phenyl}-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one



Part A. 1-(1-Bromomethylcyclopropyl)-4-iodobenzene (2.0 g, 5.97 mmol) and NaN_3 (1.0 g, 15.38 mmol, 2.6 eq) were stirred in DMF (10 mL) overnight. Analytical LC-MS showed completion of the reaction. EtOAc was added to the solution. The mixture was washed with H_2O and brine, dried over $MgSO_4$, and concentrated to give 1-(1-azidomethyl-cyclopropyl)-4-iodobenzene (1.43 g, yield: 80%). The azide

(1.40 g, 4.68 mmol) and PPh_3 (1.84 g, 7.02 mmol, 1.5 eq) were stirred in THF (10 mL) at RT for 40 min. H_2O (2 mL) was added, and the solution was stirred at 50°C for 6h. LC-MS showed completion of the reaction. The mixture was extracted with Et_2O (2x). The aqueous layer was basified with 50% NaOH, extracted with CH_2Cl_2 (2x), washed with H_2O, brine, dried over $MgSO_4$, and concentrated to give 1-(4-iodophenyl)cyclopropyl methylamine (0.98 g, yield: 75%).

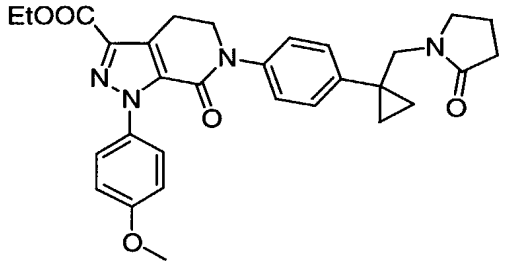
Part B. The product from Part A (0.36 g, 1.31 mmol) was stirred in dry CH_2Cl_2 (10 mL) at RT. NaOH (0.16 g, 3.93 mmol, 3 eq) was added, followed by the addition of 4-chlorobutyryl chloride (0.16 mL, 1.42 mmol). The reaction mixture was stirred at RT for 1h. It was washed with H_2O and brine, dried over $MgSO_4$, and concentrated to dryness. The residue was dissolved in THF (10 mL). K-O-tBu (0.29 g, 2.62 mmol) was added as one single portion. The mixture was stirred at 0°C under N_2 for 1h. LC-MS showed completion of the reaction. EtOAc was added. It was washed with H_2O and brine, dried over $MgSO_4$, and concentrated to produce 1-[1-(4-iodophenyl)cyclopropylmethyl]-pyrrolidin-2-one (0.36 g, yield: 86%). LC/MS (ESI^+) 342.0 $(M+H)^+$, t_R = 2.86 min (10-90% CH_3CN/H_2O in a 4-min run).

Part C. The product from Part B (0.18 g, 0.56 mmol) and 1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (0.16 g, 0.47 mmol) were stirred in DMSO (1 mL) under N_2. K_2CO_3 (0.20 g, 1.44 mmol) was added, followed by the addition of CuI (0.030 g, 20 mol%) and 1,10-phenanthroline (0.028 g, 20 mol%). The resulting mixture was heated at 120°C overnight. After cooling, it was extracted with EtOAc (2x), washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by flash column

chromatography (silica gel, CH_2Cl_2:EtOAc = 1:1, then EtOAc) to give the desired compound (83 mg, yield: 25%). LC/MS (ESI^+) 535.2 $(M+H)^+$, t_R = 3.45 min (10-90% CH_3CN/H_2O in a 6-min run). ^1H NMR (CDCl3) δ 7.45 (d, *J* = 8.8 Hz, 2H), 7.25 (AA'BB', *J* = 8.6 Hz, 4H), 6.91 (d, *J* = 9.2 Hz, 2H), 4.10 (t, *J* = 6.6 Hz, 2H), 3.80 (s, 3H), 3.68 (s, 2H), 3.46 (m, 2H), 3.29 (m, 3H), 3.23 (t, *J* = 6.6 Hz, 2H), 2.25 (m, 2H), 1.86 (m, 2H), 0.86 (m, 4H) ppm.

Example 88

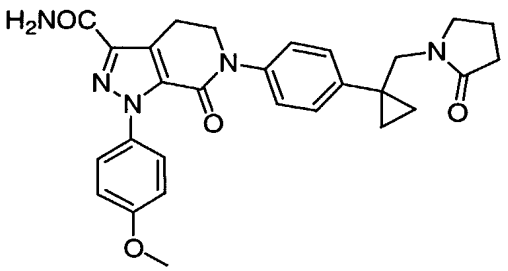
1-(4-Methoxyphenyl)-7-oxo-6-{4-[1-(2-oxo-pyrrolidin-1-ylmethyl)cyclopropyl]phenyl}-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid ethyl ester



Following a procedure analogous to that used for the preparation of Example 87, the title compound was prepared. The product was purified by silica gel column chromatography. LC/MS (ESI^+) 529.4 $(M+H)^+$, t_R = 3.14 min (25-90% CH_3CN/H_2O in a 6-min run).

Example 89

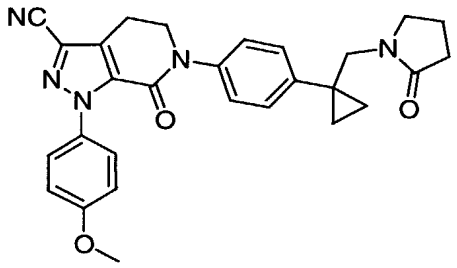
1-(4-Methoxyphenyl)-7-oxo-6-{4-[1-(2-oxo-pyrrolidin-1-ylmethyl)cyclopropyl]phenyl}-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid amide



Following a procedure analogous to that used for the preparation of Example 67, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 500.2 $(M+H)^+$, t_R = 3.28 min (10-90% CH_3CN/H_2O in a 6-min run).

Example 90

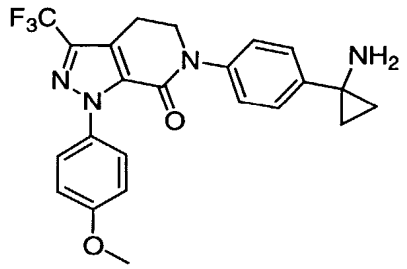
1-(4-Methoxyphenyl)-7-oxo-6-{4-[1-(2-oxo-pyrrolidin-1-ylmethyl)cyclopropyl]phenyl}-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile



Following a procedure analogous to that used for the preparation of Example 74, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). Analytical LC/MS (ESI^+) 482.4 $(M+H)^+$, t_R = 2.63 min (35-95% CH_3CN/H_2O in a 6-min run).

Example 91

6-[4-(1-Aminocyclopropyl)phenyl]-1-(4-methoxyphenyl)-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt

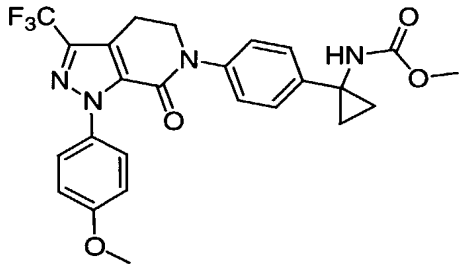


The product of Part D in Example 1 (ca. 0.50 g) was stirred in dry toluene at RT. DPPA (0.25 mL) was added, followed by the addition of Et_3N (0.35 mL). The resulting mixture

was stirred at 100°C for 3h. After cooling to RT, 8N HCl (10 mL) was added. The resulting mixture was heated at 100°C overnight. The cooled mixture was extracted with Et_2O (2x). The aqueous layer was basified with 50% NaOH. The mixture was extract with chloroform (2x). The organics were washed with H_2O and brine, dried over $MgSO_4$, and concentrated to dryness. The residue was dissolved in MeOH, and purified by prep LC/MC (5-98% CH_3CN/H_2O in a 10-min run) to give the desired product. Analytical LC/MS (ESI^+) 443.2 $(M+H)^+$, t_R = 2.69 min (35-95% CH_3CN/H_2O in a 6-min run).

Example 92

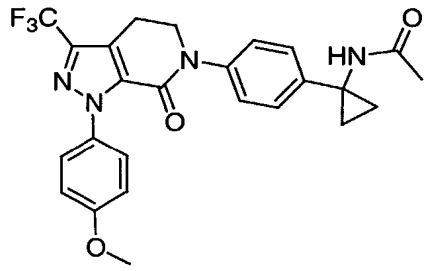
(1-{4-[1-(4-Methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropyl)-carbamic acid methyl ester



Following a procedure analogous to that used for the preparation of Example 91, the title compound was prepared by using MeOH instead of conc. HCl as the solvent. Silica gel purification yielded the pure desired product. LC/MS (ESI^+) 501.6 $(M+H)^+$, t_R = 3.19 min (35-95% CH_3CN/H_2O in a 6-min run). ^1H NMR ($CDCl_3$) δ 7.46 (d, J = 8.8 Hz, 2H), 7.24 (m, 4H), 6.91 (d, J = 9.2 Hz, 2H), 4.12 (t, J = 6.6 Hz, 2H), 3.81 (s, 3H), 3.64 (s, 2H), 3.14 (t, J = 6.6 Hz, 2H), 1.22 (m, 4H) ppm.

Example 93

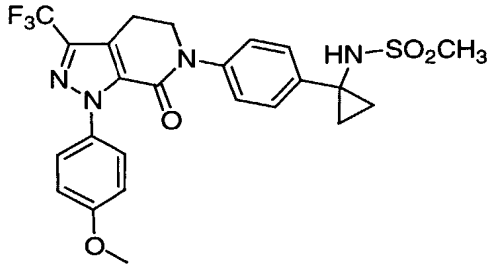
***N*-(1-{4-[1-(4-Methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}-cyclopropyl)-acetamide**



Following a procedure analogous to that used for the preparation of Example 21, the title compound was prepared. Silica gel purification yielded the pure desired product. LC/MS (ESI$^+$) 485.2 (M+H)$^+$, t_R = 3.06 min (35-95% CH_3CN/H_2O in a 6-min run). ^1H NMR ($CDCl_3$) δ7.46 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H), 6.94 (AA'BB', J = 9.1 Hz, 4H), 4.09 (m, 2H), 3.81 (m, 2H), 3.14 (t, J = 6.6 Hz, 2H), 2.38 (s, 3H), 1.57 (m, 2H), 1.40 (m, 2H) ppm.

Example 94

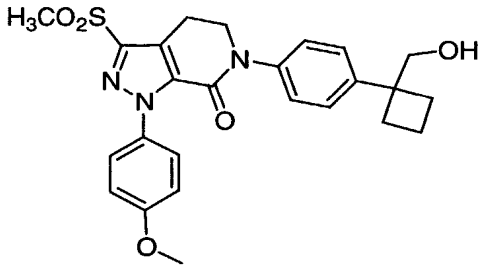
***N*-(1-{4-[1-(4-Methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}-cyclopropyl)-methanesulfonamide**



Silica gel purification yielded the pure desired product. LC/MS (ESI$^+$) 521.2 (M+H)$^+$, t_R = 3.14 min (35-95% CH_3CN/H_2O in a 6-min run). ^1H NMR ($CDCl_3$) δ 7.46 (d, J = 9.2 Hz, 2H), 7.35 (AA'BB', J = 8.8 Hz, 4H), 6.92 (d, J = 8.8 Hz, 2H), 5.19 (s, 1H), 4.13 (t, J = 6.6 Hz, 2H), 3.81 (s, 3H), 3.16 (t, J = 6.6 Hz, 2H), 1.26 (m, 2H), 1.18 (m, 2H) ppm.

Example 95

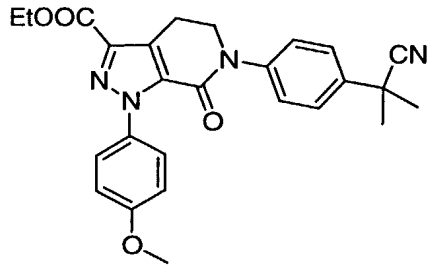
6-[4-(1-Hydroxymethylcyclopropyl)phenyl]-3-(methanesulfonyl)-1-(4-methoxyphenyl)-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one



Following a procedure analogous to that used for the preparation of product of Part C in Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 481.4 $(M+H)^+$, t_R = 5.51 min. ^1H NMR (acetone-d_6) δ 7.53 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 4.14 (t, J = 6.6 Hz, 2H), 3.83 (m, 4H), 3.63 (s, 2H), 3.27 (t, J = 6.6 Hz, 2H), 3.26 (s, 3H), 2.02 (m, 4H), 1.81 (m, 2H) ppm.

Example 96

Ethyl 6-[4-(cyano-dimethyl-methyl)phenyl]-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboylate



Part A. To 4-iodobenzylbromide (25 g, 84 mmol) in boiling EtOH (100 mL) was added potassium cyanide (8.2 g, 126 mmol) through the condenser. The reaction was heated 24h, then

cooled and EtOH removed. The aqueous layer was extracted with EtOAc and dried (Na_2SO_4) to afford crude 4-iodobenzylnitrile. The 4-iodobenzylnitrile was first treated with HCl gas in MeOH to afford conversion to the ester. The mixture was concentrated in vacuo and treated with MeOH (4.7 mL) and chlorotrimethylsilane (10.7 mL) at 50^0C for 4h. The reaction was cooled and quenched with H_2O (3.5 mL). Dichloromethane (150 mL) was added followed by Na_2CO_3 (8.9 g) and the mixture was stirred at room temperature for 1h. The organics were separated and dried (Na_2SO_4), filtered, and concentrated to afford 21 g crude (4-iodo-phenyl)-acetic acid methyl ester. ^1H NMR ($CDCl_3$) δ 7.66 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 3.69 (s, 3H), 3.56 (s, 2H) ppm.

Part B. To a THF (100 mL) solution containing sodium hydride (9.5 g, 0.23 mol) at 0^0C was added dropwise crude methyl-(4-iodo-phenyl)-acetic acid methyl ester (21 g, 79 mmol, from Part A in THF (50 mL). After the addition was complete, methyl iodide (11.4 mL, 0.18 mol) in THF (20 mL) was added and the reaction was stirred 72h at rt. The reaction mixture was quenched with ice water followed by extraction with EtOAc. Drying with Na_2SO_4 afforded 27 g of a crude mixture of two products. Purification by chromatography on silica gel (10:1 hexanes/ethyl acetate) afforded 5 g pure methyl 2-(4-iodophenyl)-2-methyl propronate and 10 g mixture of the desired ester and 2-(4-iodophenyl)-2-methylproprionitrile. ^1H NMR for methyl 2-(4-iodophenyl)-2-methyl propronate ($CDCl_3$) δ 7.65 (d, J = 8.5, 2H), 7.09 (d, J = 8.8 Hz, 2H), 3.64 (s, 3H), 1.54 (s, 6H) ppm.

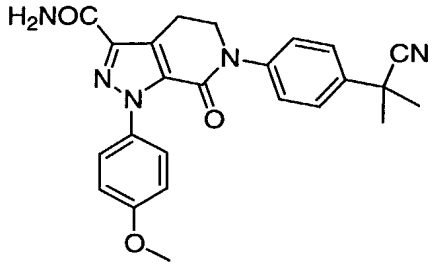
Part C. To 8 g of the crude mixture from Part B in THF (75 mL) and H_2O (25 mL) was added LiOH (3 g), and the reaction

was stirred overnight. Acid/base extraction afforded 3.6 g of 2-(4-iodophenyl)2-methylproprionic acid, Mass Spec $(M+H)^+$ 290.8 and 5.3 g of 2-(4-iodophenyl)2-methylproprionitrile. IR(KBr) CN at 2236.66.

Part D. To a DMSO (4 mL, degassed) solution of ethyl 1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (0.6 g, 1.9 mmol), and 2-(4-iodophenyl) 2-methylproprionitrile (0.6 g, 2.2 mmol), and K_2CO_3 (0.66 g, 4.8 mmol) and was added CuI (73 mg, 0.3 mmol). The reaction was heated to 130^{0}C for 18h. The reaction was cooled, extracted with EtOAc, washed with H_2O, and dried ($MgSO_4$). Purification by chromatography on silica gel (1:1 hexanes/ethyl acetate) afforded the title compound 0.4 g (45.9%) of a pale yellow solid; Mass Spec $(M+H)^+$ 459.3.

Example 97

6-[4-(1-cyano-1-methylethyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pryidine-3-carboxamide

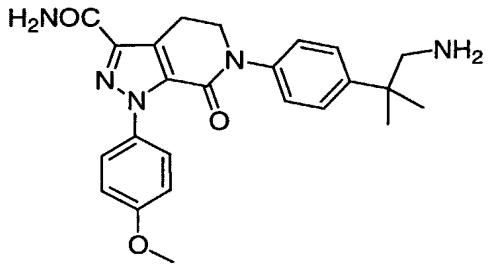


Ethyl 6-[4-(cyano-dimethyl-methyl)phenyl]-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboyla te (0.38 g, 0.83 mmol) obtained in Example 96 was placed in a sealed tube containing 10% ammonia in ethylene glycol (3 mL) and heated 80^{0}C for 2h. The reaction was cooled, quenched with H_2O, extracted with EtOAc, and dried ($MgSO_4$). Recrystallization from

CH_2Cl_2/Hexanes afforded 0.31g (88%) of the title amide. High Resolution Mass Spec $(M+H)^+$ for $C_{24}H_{24}N_5O_3$ 430.1898.

Example 98

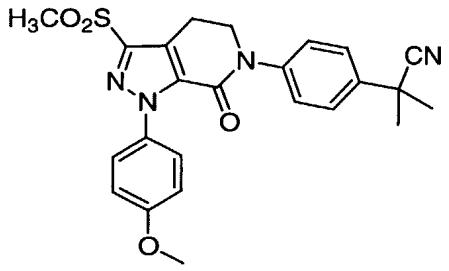
6-[4-(2-Amino-1,1-dimethylethyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide



6-[4-(1-Cyano-1-methylethyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pryidine-3-carboxamide (0.1 g) was hydrogenated at 40psi in EtOH/HCl with 20 mg 10%Pd/C and purified by HPLC to afford 70 mg (56%) of title amine. High Resolution Mass Spec $(M+H)^+$ for $C_{24}H_{28}N_5O_3$ 434.2176.

Example 99

1-{4-[(1-methoxyphenyl)-3-(methylsulfonyl)-7-oxo-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridinyl-6-yl]phenyl}-2-methylpropanenitrile

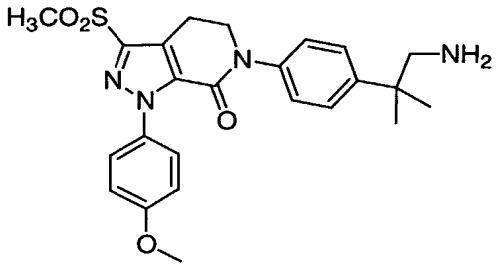


To a degassed DMSO (4 mL) solution containing 1-(4-methoxyphenyl)-3-methylsulfonyl-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (0.6 g, 1.8 mmol) and 2-(4-iodophenyl)2-methylproprionitrile (0.6 g, 2.2 mmol) was

added K_2CO_3 (0.64 g, 4.6 mmol) and CuI (71 mg, 0.3 mmol). The reaction was heated to 130^{0}C for 18h. The reaction was cooled, extracted with EtOAc, washed with H_2O, and dried ($MgSO_4$). Purification by chromatography on silica gel (1:1 hexanes/ethyl acetate) afforded 0.52 g (61%) of a pale yellow foam; High Resolution Mass Spec $(M+H)^+$ for $C_{24}H_{25}N_4O_4S$ 456.1624.

Example 100

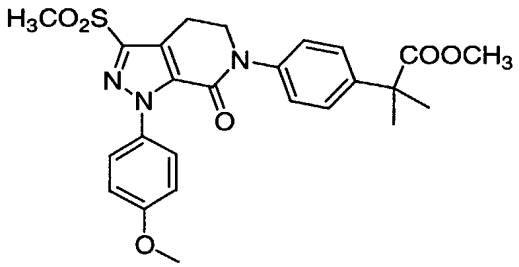
6-[4-(2-amino-1,1-dimethyl)phenyl]-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one



1-{1-[(4-Methoxyphenyl)-3-(methylsulfonyl)-7-oxo-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridinyl-6-yl]phenyl}-2-methylpropanenitrile (0.1 g) was hydrogenated at 40psi in EtOH/HCl with 20 mg 10%Pd/C and purified by HPLC to afford 85 mg (68%) of the title amine. High Resolution Mass Spec $(M+H)^+$ for $C_{24}H_{28}N_4O_4S$ 469.1907.

Example 101

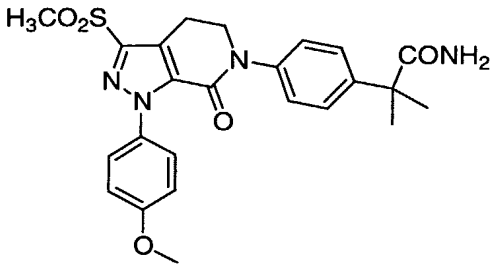
Preparation of 2-{4-[3-methanesulfonyl-1-(4-methoxyphenyl)-7-oxo-1,4,5,7-tetrahydropyrazolo[3,4-*c*]pyridin-6-yl]phenyl}-2-methylproprionic acid methyl ester



To a degassed DMSO (4 mL) solution was added ethyl 1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylate (0.4 g, 1.2 mmol) and methyl 2-(4-iodophenyl)2-methyl propronate (0.53 g, 1.7 mmol) was added K_2CO_3 (0.43 g, 3.1 mmol) and CuI (47 mg, 0.25 mmol). The reaction was heated to 130^{0}C for 18h, cooled, extracted with EtOAc, washed with H_2O, and dried ($MgSO_4$). Purification by chromatography on silica gel (1:1 hexanes/ethyl acetate) afforded the titled compound 0.43 g (45.9%) of a pale yellow foam. High Resolution Mass Spec $(M+H)^+$ for $C_{25}H_{28}N_3O_6S$ 498.1691.

Example 102

2-{4-[1-(4-methoxypheny)-3-(methylsulfonyl)-7-oxo-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}-2-methylpropnamide

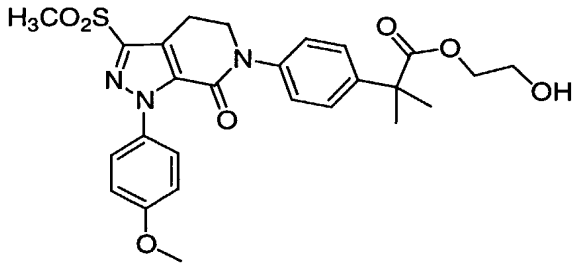


2-{4-[3-Methanesulfonyl-1-(4-methoxyphenyl)-7-oxo-1,4,5,7-tetrahydropyrazolo[3,4-*c*]pyridin-6-yl]phenyl}-2-methylproprionic acid methyl ester (0.095 g, 0.19 mmol) was placed in a sealed tube containing 10% ammonia in ethylene glycol (3 mL) and heated 80^{0}C for 18h. The reaction was cooled, quenched with H_2O, extracted with EtOAc, and dried

($MgSO_4$). Purification by HPLC afforded 35 mg (36%) title compound; High Resolution Mass Spec $(M+H)^+$ for $C_{24}H_{27}N_4O_5S$ 483.1725.

Example 103

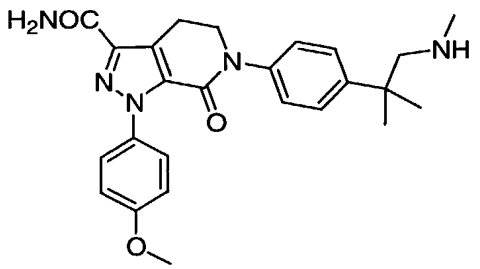
2-Hydroxyethyl-2-{4-[1-(4-methoxypheny)-3-(methlysulfonyl)-7-oxo-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl]phenyl]-2-methylpropanoate



2-{4-[3-Methanesulfonyl-1-(4-methoxyphenyl)-7-oxo-1,4,5,7-tetrahydropyrazolo[3,4-*c*]pyridin-6-yl]phenyl}-2-methylproprionic acid methyl ester (0.077 g, 0.15 mmol) was placed in a sealed tube containing 10% ammonia in ethylene glycol (3 mL) and heated 80^0C for 2h. The reaction was cooled, quenched with H_2O, extracted with EtOAc, and dried ($MgSO_4$). Purification by chromatography on silica (1:1 hexanes/ethyl acetate) and then HPLC purification afforded 27 mg (33%) title compound. High Resolution Mass Spec $(M+H)^+$ for $C_{26}H_{30}N_3O_7S$ 528.1776.

Example 104

6-{4-[1,1-dimethyl-2-(methylamino)ethyl]phenyl}-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide



Part A. To ethyl 1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylate (2.35 g, 7.5 mmol) and 2-(4-iodophenyl)2-methylproprionic acid (2.6 g, 8.9 mmol) was added K_2CO_3 (3.1 g, 0.022 mol), DMSO (4 mL), and CuI (0.28 mg, 1.4 mmol). The reaction was heated to 130^{0}C for 18h cooled, extracted with EtOAc, washed with H_2O, and dried ($MgSO_4$). Purification by chromatography on silica gel (5%MeOH/CH_2Cl_2) afforded 1.1 g product.

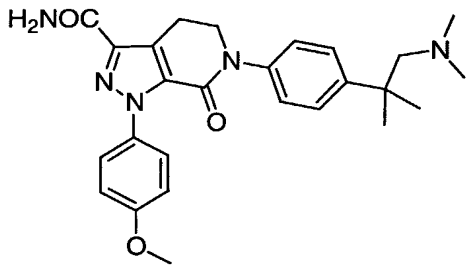
Part B. To the acid from Part A (1 g, 2 mmol) in THF (30 mL) at 0^{0}C was added 1M Borane in THF (2.5 mL, 2.5 mmol) and the reaction was allowed to stir 18h. The reaction was extracted with EtOAc, washed with brine, and dried (Na_2SO_4) to afford crude alcohol. To the alcohol was added CH_2Cl_2 (100 mL), molecular sieves, sodium acetate (0.17 g, 2 mmol), and pyridinium chlorochromate (0.72 g, 3.3 mmol) and the reaction was stirred 24h. After dilution with Et_2O, filtration through paper, and concentration, the crude residue was purified by chromatography on silica gel (2:1 hexanes/EtOAc) to afford 0.527 g of the desired aldehyde. ^{1}H NMR ($CDCl_3$) δ 9.46 (s, 1H), 7.48 (d, J = 9.2 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 9.1 Hz, 2H), 6.92 (d, J = 9.2 Hz, 2H), 4.49 (q, J = 7 Hz, 2H), 4.13 (t, J = 6.6 Hz, 2H), 3.80 (s, 3H), 3.35 (t, J = 6.6 Hz, 2H), 1.45 (t, J = 7.3 Hz, 3H) ppm.

Part C. To the aldehyde from Part B (95 mg, 0.2 mmol) in 1:1 THF/MeOH (5 mL) was added excess 33% methylamine in EtOH (0.1 mL). After 15 min 0.5M $ZnCl_2$ in THF (0.2 mL, 0.1 mmol) followed by sodium cyanoborohydride (13 mg, 0.2 mmol) were added. The reaction was stirred 24h. The solvents were removed and the residue was partitioned between EtOAc and H_2O. Extraction with EtOAc and drying ($MgSO_4$) afforded crude ester/amine.

Part D. The ester/amine from Part C was heated in a sealed tube containing 2 mL of 10% NH_3/ethylene glycol at 80°C for 2h. After cooling the product was extracted by EtOAc, washed with water and dried ($MgSO_4$). Purification by HPLC and freeze-drying afforded the titled compound 78 mg (69%) as a white solid. High Resolution Mass Spec $(M+H)^+$ for $C_{25}H_{30}N_5O_3$ 448.2337.

Example 105

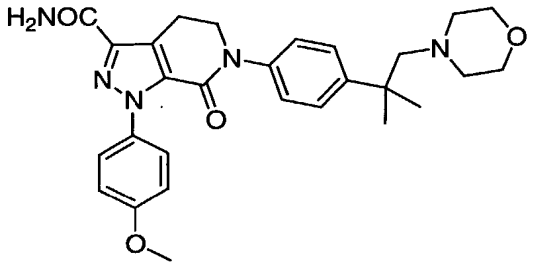
6-{4-[2-dimethylamino)-1,1-dimethylethyl]phenyl}-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide



Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec $(M+H)^+$ for $C_{26}H_{32}N_5O_3$ 462.2529.

Example 106

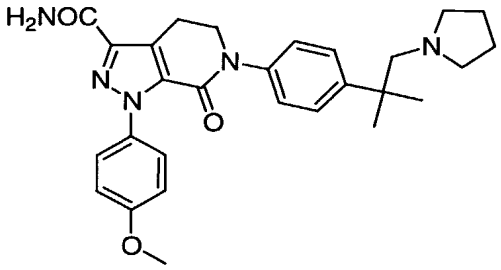
6-{4-[1,1-dimethyl-2-(1-morpholinyl)ethyl]phenyl}-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-*1H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide



Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec $(M+H)^+$ for $C_{28}H_{34}N_5O_4$ 504.2637.

Example 107

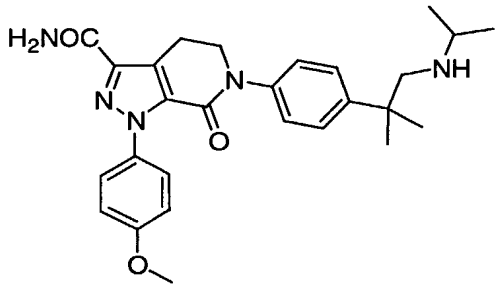
6-{4-[1,1-dimethyl-2-(1-pyrrolidinyl)ethyl]phenyl}-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide



Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec $(M+H)^+$ for $C_{28}H_{34}N_5O_3$ 488.2667.

Example 108

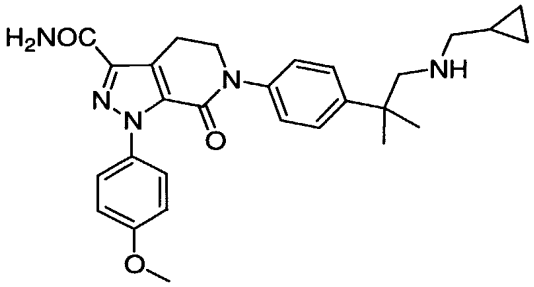
6-{4-[2-(isopropylamino)1,1-dimethylethyl]phenyl}-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-*1H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide



Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec $(M+H)^+$ for $C_{27}H_{34}N_5O_3$ 476.2666.

Example 109

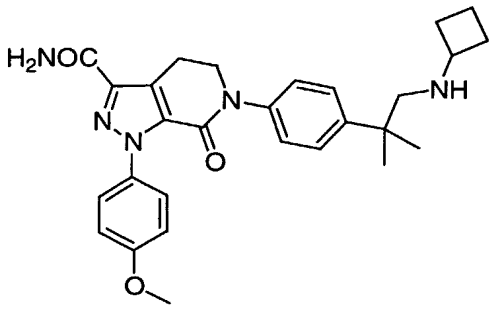
6-(4-{2-[(cyclopropylmethyl)amino]-1,1-dimethylethyl}phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-*1*H-pyrazolo[3,4-*c*]pyridine-3-carboxamide



Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec $(M+H)^+$ for $C_{28}H_{33}N_5O_3$ 488.2670.

Example 110

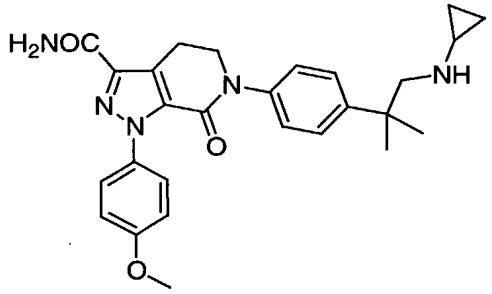
6-{4-[2-(cyclobutylamino)1,1-dimethylethyl]phenyl}-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-*1*H-pyrazolo[3,4-*c*]pyridine-3-carboxamide



Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec $(M+H)^+$ for $C_{28}H_{34}N_5O_3$ 488.2668.

Example 111

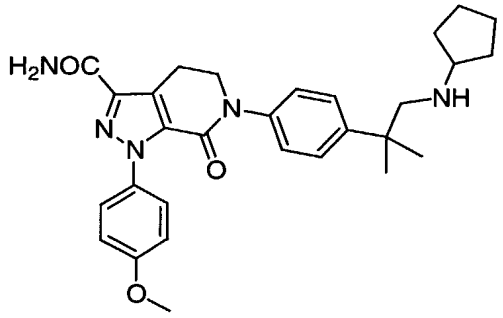
6-{4-[2-(cyclopropylamino)1,1-dimethylethyl]phenyl}-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide



Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec $(M+H)^+$ for $C_{27}H_{32}N_5O_3$ 474.2513

Example 112

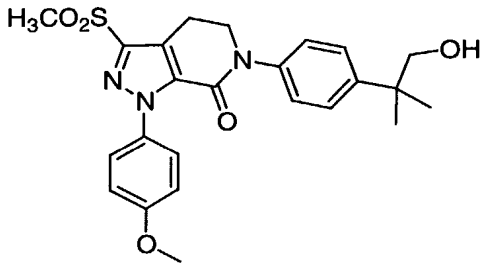
6-{4-[2-(cyclopentylamino)1,1-dimethylethyl]phenyl}-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide



Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec $(M+H)^+$ for $C_{29}H_{36}N_5O_3$ 502.2814.

Example 113

6-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,7-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one



Part A. To crude 2-{4-[3-methanesulfonyl-1-(4-methoxyphenyl)-7-oxo-1,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]phenyl}-2-methylproprionic acid methyl ester (2 g, 0.4 mmol) was added LiOH (0.5 g, 12 mmol) in THF/MeOH/H_2O for 24h. The reaction was acidified with 1N HCl and extracted with EtOAc and concentrated to afford crude acid as a semi solid mass.

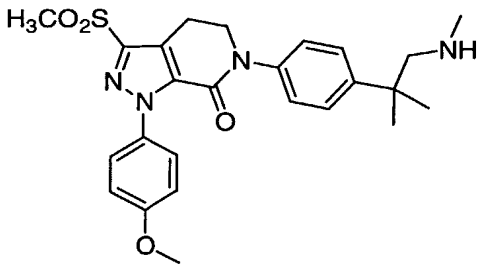
Part B. The crude acid from Part A was then reduced with 1M borane in THF (7.3 mL, 7.3 mmol) in THF (25 mL) over 24h. The reaction was quenched with water and extracted with EtOAc and dried ($MgSO_4$) to afford the corresponding alcohol.

Part C. The crude alcohol from Part B (2.3 g, 4.9 mmol) was oxidized with pyridinium chlorochromate (1.7 g, 7.8 mmol), sodium acetate (0.4 g, 4.9 mmol), and molecular sieves in CH_2Cl_2 for 24h. Dilution with diethyl ether and filtration followed by chromatography on silica gel (1:1 hexanes/EtOAc) afforded 0.6 g (27%) of aldehyde; ^1H NMR $CDCl_3$ δ 9.46 (s, 1H), 7.48 (d, J = 8.8 Hz, 2H), 7.31 (m, 4H), 6.94 (d, J = 8.8 Hz, 2H), 4.15 (t, J = 6.6 Hz, 2H), 3.81 (s, 3H), 3.36 (t, J = 6.6 Hz, 2H), 3.31 (s, 3H), 1.44 (s, 6H) ppm.

Part D. To the aldehyde from Part C (34 mg, 0.072 mmol) was added 2-aminoimidazole sulfate (19 mg, 0.144 mmol) in 1:1 THF/MeOH (5 mL) followed by 0.5M $ZnCl_2$ (0.05 mL, 0.027 mmol) and 1M sodium cyanoborohydride in THF (0.07 mL, 0.07 mmol) and the reaction was stirred 24h. The reaction was quenched with water, extracted with EtOAc, and dried ($MgSO_4$). Purification by HPLC and freeze-drying afforded 12 mg (35%) of the desired alcohol: ^1H NMR ($CDCl_3$) δ 7.48 (d, *J* = 9.2 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 9.1 Hz, 2H), 4.15 (t, *J* = 6.6 Hz, 2H), 3.81 (s, 3H), 3.61 (s, 2H), 3.34 (t, *J* = 6.6 Hz, 2H), 3.31 (s, 3H), 1.31 (s, 6H)ppm.

Example 114

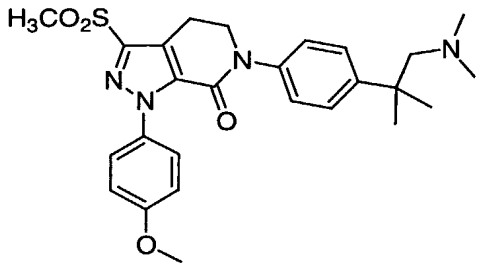
6-{4-[1,1-dimethyl-2-(methylamino)ethyl]phenyl}-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,7-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one



Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec $(M+H)^+$ for $C_{25}H_{31}N_4O_4S$ 483.2049.

Example 115

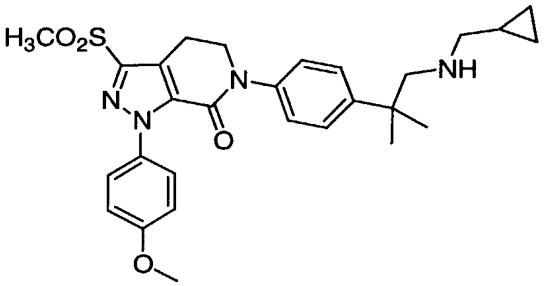
6-{4-[2-(dimethylamino) 1,1-dimethylethyl]phenyl}-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,7-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one



Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec $(M+H)^+$ for $C_{26}H_{33}N_4O_4S$ 497.2201.

Example 116

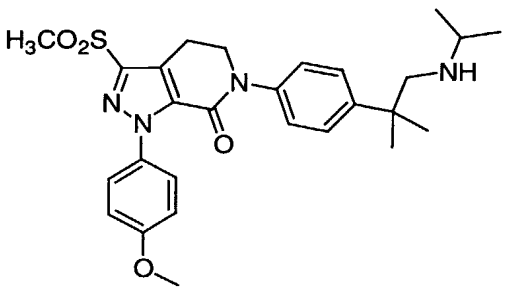
6-(4-{2-[(cyclopropylmethyl)amino]-1,1-dimethylethyl}phenyl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,7-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one



Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec $(M+H)^+$ for $C_{28}H_{35}N_4O_4S$ 523.2362.

Example 117

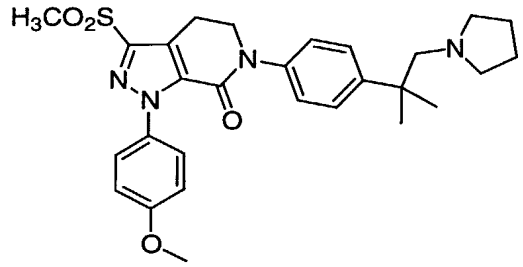
6-{4-[1,1-dimethyl-2-(isopropylamino)ethyl]phenyl}-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,7-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one



Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec $(M+H)^+$ for $C_{27}H_{35}N_4O_4S$ 511.2379.

Example 118

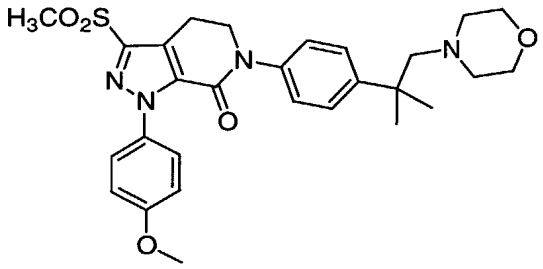
6-{4-[1,1-dimethyl-2-(1-pyrrolidinyl)ethyl]phenyl}-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,7-tetrahydro-7*H*-pyrazolo[3,4-*c*] pyridin-7-one



Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec $(M+H)^+$ for $C_{28}H_{35}N_4O_4S$ 523.2388.

Example 119

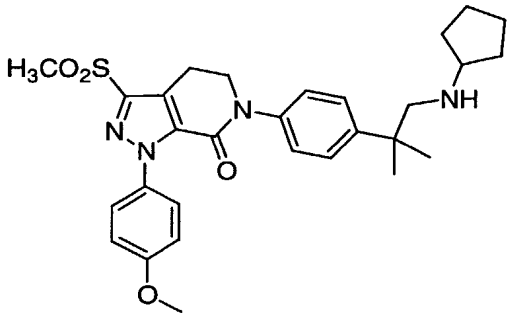
6-{4-[1,1-dimethyl-2-(1-morpholinyl)ethyl]phenyl}-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,7-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one



Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec $(M+H)^+$ for $C_{28}H_{35}N_4O_5S$ 539.2342.

Example 120

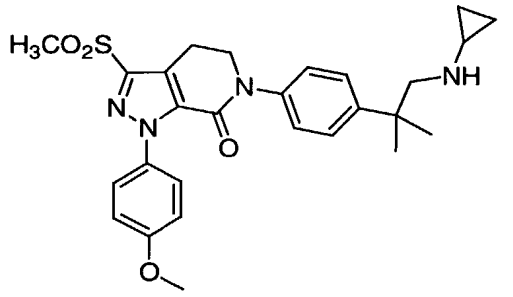
6-{4-[2-(cyclopentylamino) 1,1-dimethylethyl]phenyl}-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,7-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one



Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec $(M+H)^+$ for $C_{29}H_{37}N_4O_4S$ 537.2539.

Example 121

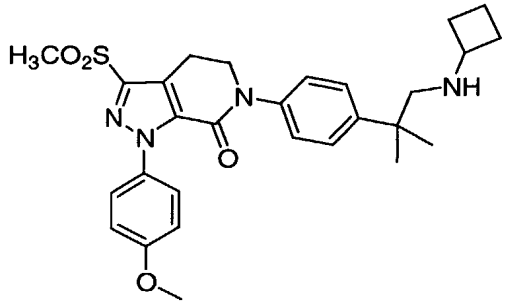
6-(4-{2-{(cyclopropylamino) 1,1-dimethylethyl]phenyl}-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,7-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one



Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec $(M+H)^+$ for $C_{27}H_{33}N_4O_4S$ 509.2227.

Example 122

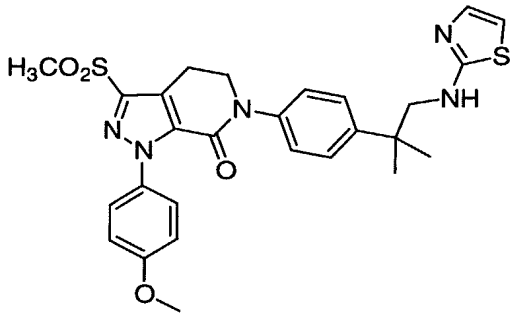
6-{4-[2-(cyclobutylamino) 1,1-dimethylethyl]phenyl}-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,7-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one



Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec $(M+H)^+$ for $C_{28}H_{35}N_4O_4S$ 523.238.

Example 123

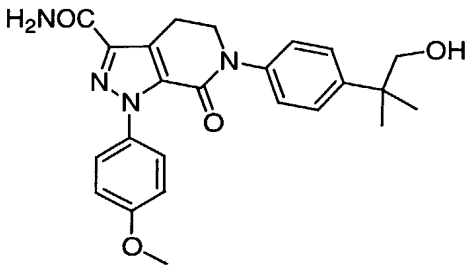
6-{4-[1,1-dimethyl-2-(1,3-thiazol-2yl amino)ethyl]phenyl}-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,7-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one



Prepared as previously described above. High Resolution Mass Spec $(M+H)^+$ for $C_{27}H_{30}N_5O_4S_2$ 552.1727.

Example 124

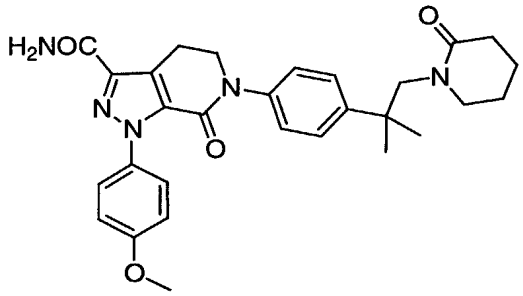
6-[4-(2-hydroxy-1,1-dimethylethyl)phenyl}-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide



Following a procedure analogous to that used in Example 113, the title compound was prepared. High Resolution Mass Spec $(M+H)^+$ for $C_{24}H_{27}N_4O_4$ 435.2016.

Example 125

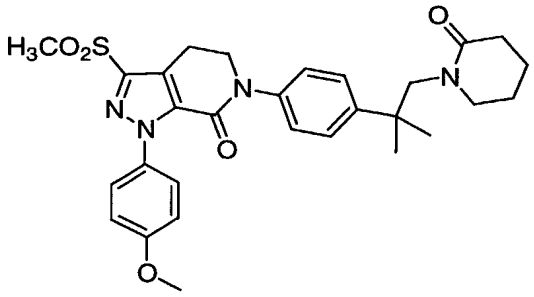
6-{4-[1,1-dimethyl-2-(2-oxo-1-piperidinyl)ethyl]phenyl}-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*- pyrazolo [3,4-*c*]pyridine-3-carboxamide



To 6-[4-(1-cyano-1-methylethyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pryidine-3-carboxamide (0.17 g,0.39 mmol) was hydrogenated at 40psi in ethanol with 0.5 mL conc. HCl and 10% palladium on carbon (25 mg) for 72h. The reaction was filtered and concentrated. To the amine in THF (5 mL) at 0^0C was added 5-bromovaleryl chloride (99 mg, 0.5 mmol) and TEA (1 mL) and the reaction was stirred 1h. To the reaction was added potassium *t*-butoxide (0.24 g, 1.9 mmol) and the reaction was stirred 24h. The reaction was quenched with water and extracted with ethyl acetate and dried ($MgSO_4$). Purification by HPLC and freeze-drying afforded 15 mg (7.5%). Mass Spec $(M+H)^+$ 516.3.

Example 126

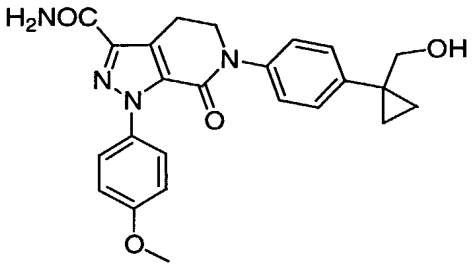
6-{4-[1,1-dimethyl-2-(2-oxo-1-piperidinyl)ethyl]phenyl}-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one



1-{4-[(1-Methoxyphenyl)-3-(methylsulfonyl)-7-oxo-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridinyl-6-yl] phenyl}-2-methylpropanenitrile was converted into the target compound by the same procedure as that of Example 125. Mass Spec $(M+H)^+$ 551.3.

Example 127

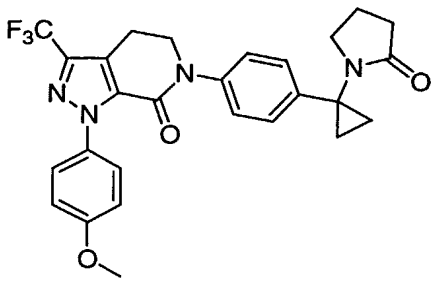
6-[4-(1-Hydroxymethylcyclopropyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylic acid amide



Following a procedure analogous to that used in Example 95, the title compound was prepared. LC/MS (ESI^+) 433.4 $(M+H)^+$.

Example 128

1-(4-Methoxyphenyl)-6-{4-[1-(2-oxo-pyrrolidin-1-yl)-cyclopropyl]phenyl}-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one



Part A. 4-Iodophenylcyclopropyl carboxylic acid (7.42 g, 25.76 mmol) was stirred in CH_2Cl_2 (60 mL) at rt under N_2. Et_3N (5.4 mL, 38.64 mmol, 1.5 eq) was added followed by the addition of DPPA (8.27 mL, 38.64 mmol, 1.5 eq). The resulting mixture was stirred at rt overnight. It was poured into ice H_2O (100 mL), acidified with 6N HCl, and then extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The oil residue obtained was dissolved in *t*-BuOH (40 mL) and refluxed for 2-3 h. After cooling, the solvent was evaporated. The residue was purified by FCC (silica gel, hexane: CH_2Cl_2=1:1, then CH_2Cl_2, then CH_2Cl_2:MeOH=100:1 to 25:1) to give pure [1-(4-iodophenyl)-cyclopropyl]-carbamic acid *tert*-butyl ester (6.01 g, yield: 65%). This compound (2.12 g, 5.89 mmol) was stirred in CH_2Cl_2 (10 mL) and TFA (10 mL) at rt for 2h. After evaluation, the residue was taken up in $CHCl_3$ (100 mL) and H_2O (100 mL). The aqueous layer was basified with K_2CO_3, extracted with $CHCl_3$ (2 x), dried over $MgSO_4$, filtered, and concentrated to dryness to give pure 1-(4-iodophenyl)cyclopropylamine (1.50 g, yield: 98%). ^1H NMR ($CDCl_3$) δ 7.62 (m, 2H), 7.06 (m, 2H), 1.88 (m, 2H), 1.07 (m, 2H), 0.95 (m, 2H) ppm. HRMS $C_9H_{11}IN$ $(M+H)^+$ 259.9930 calcd for 259.9936.

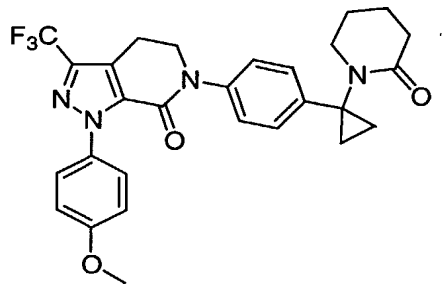
Part B. The mixture of the product from Part A (0.32 g, 1.24 mmol), NaOH (0.15 g, 3.72 mmol, 3.0 eq), and 4-chlorobutyryl chloride (0.18 mL, 1.61 mmol, 1.3 eq) was stirred in CH_2Cl_2 (7 mL) at rt for 1 h under N_2. H_2O was added. It was extracted with EtOAc (2x), washed with H_2O and brine, dried over $MgSO_4$, and concentrated to dryness. The residue was dissolved in THF (10 mL). KO*t*Bu (0.40 g, 4.16 mmol) was added as one portion. The mixture was

stirred at 0°C under N_2 for 30 min. EtOAc was added. It was washed with H_2O and brine, dried over $MgSO_4$, and concentrated to produce 1-[1-(4-iodophenyl)cyclopropyl]-pyrrolidin-2-one (0.27 g, yield: 100%). ^1H NMR ($CDCl_3$) δ 7.68 (d, *J*=8.5 Hz, 2H), 6.87 (d, *J*=8.5 Hz, 2H), 3.26 (t, *J*=7.3 Hz, 2H), 2.26 (t, *J*=7.6 Hz, 2H) 1.88 (t, *J*=7.0 Hz, 2H), 1.22 (m, 2H), 1.10 (m, 2H) ppm.

Part C. The product from Part B (64 mg, 0.196 mmol) and 1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (0.061 g, 0.196 mmol) were stirred in DMSO (0.3 mL) under N_2. K_2CO_3 (0.067 g, 0.49 mmol, 2.5 eq) was added, followed by the addition of CuI (0.037 g, 0.194 mmol) and 1,10-phenanthroline (0.020 g, 0.108 mmol). The resulting mixture was heated at 120°C for 3h. After cooling, it was extracted with EtOAc (2x), washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by FCC (silica gel, CH_2Cl_2:EtOAc=1:1, then EtOAc) to give 1-(4-methoxyphenyl)-6-{4-[1-(2-oxo-pyrrolidin-1-yl)-cyclopropyl]phenyl}-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one (45 mg, yield: 45%). ^1H NMR ($CDCl_3$) δ 7.46 (d, *J*=8.8 Hz, 2H), 7.25 (AA'BB', *J*=8.6 Hz, 4H), 6.91 (d, *J*=9.2 Hz, 2H), 4.10 (t, *J*=6.6 Hz, 2H), 3.81 (s, 3H), 3.38 (t, *J*=7.2 Hz, 2H), 3.14 (t, *J*=6.6 Hz, 2H), 2.37 (t, *J*=7.7 Hz, 2H), 1.98 (q, *J*=7.7 Hz, 2H), 1.32 (m, 2H), 1.21 (m, 2H) ppm. HRMS $C_{27}H_{26}F_3N_3O_4$ $(M+H)^+$ 511.1931 calcd for 511.1958.

Example 129

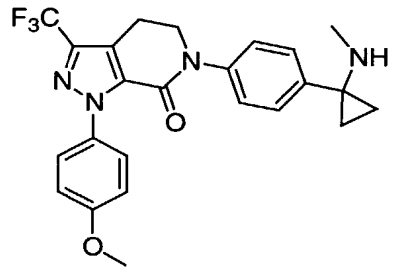
1-(4-Methoxyphenyl)-6-{4-[1-(2-oxo-piperidin-1-yl)-cyclopropyl]phenyl}-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one



Following the procedures analogous to those used in Example 128, the title compound was prepared. The product was purified by RP-prep LC-MS (35-98% CH_3CN/H_2O in a 10-min run). HRMS $C_{29}H_{32}O_2F_3N_4$ $(M+H)^+$ 525.2486 calcd for 525.2477. ^1H NMR ($CDCl_3$) δ 7.46 (d, *J*=8.8 Hz, 2H), 7.25 (d, *J*=8.4 Hz, 2H), 6.91 (d, *J*=9.2 Hz, 2H), 4.10 (t, *J*=6.6 Hz, 2H), 3.82 (s, 3H), 3.37 (t, *J*=6 Hz, 2H), 3.15 (t, *J*=6.6 Hz, 2H), 2.51 (t, *J*=6 Hz, 2H), 1.79 (m, 4H), 1.33 (m, 2H), 1.29 (m, 2H) ppm.

Example 130

1-(4-Methoxyphenyl)-6-[4-(1-methylaminocyclopropyl)-phenyl]-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one



Part A. 1-(4-Iodophenyl)cyclopropyl-carbamic acid *tert*-butyl ester (2.14 g, 5.85 mmol) was stirred in THF (20 mL) at 0°C under N_2. MeI (3 mL) was added followed by portionwise addition of NaH (2.34 g, 5 eq). The reaction was stirred at rt overnight. Several drops of H_2O and EtOAc (20 mL) were added to quench the reaction. The organic solvent was evaporated, and H_2O was added. It was extracted with Et_2O (2x), washed with brine, dried over

$MgSO_4$, and concentrated to dryness. The residue was purified by FCC (silica gel, CH_2Cl_2:hexanes=0:1 to 1:1 to 1:0) to give pure [1-(4-iodophenyl)cyclopropyl]-methyl-carbamic acid *tert*-butyl ester as a white solid (2.07 g, yield 95%). LC/MS (ESI^+) 373.8 (M+H), t_R=2.95 min (10-90% CH_3CN in H_2O in a 4-min run).

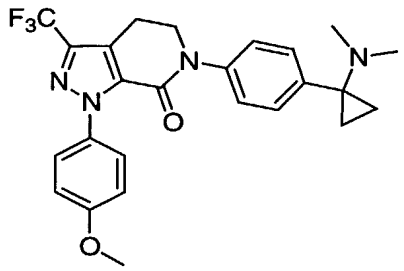
Part B. The product from Part A (205 mg, 0.55 mmol) and 1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (170 mg, 0.55 mmol) were stirred in DMSO (0.4 mL) under N_2. K_2CO_3 (250 mg, 1.81 mmol, 3.3 eq) was added, followed by the addition of CuI (52 mg, 0.27 mmol, 0.5 eq) and 1,10-phenanthroline (50 mg, 0.27 mmol, 0.5 eq). The resulting mixture was heated at 120°C for 2h. After cooling, it was extracted with EtOAc (2x), washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2:EtOAc=1:1, then EtOAc) to give (1-{4-[1-(4-methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropyl)-methyl-carbamic acid *tert*-butyl ester (250 mg, yield: 82%). ^1H NMR ($CDCl_3$) δ 7.46 (d, *J*=9.2 Hz, 2H), 7.23 (d, *J*=8.4 Hz, 2H), 7.09 (m, 2H), 6.91 (d, *J*=9.1 Hz, 2H), 4.12 (t, *J*=6.6 Hz, 2H), 3.81 (s, 3H), 3.15 (t, *J*=6.6 Hz, 2H), 2.90 (s, br, 3H), 1.42 (s, br, 9H), 1.33 (m, 2H), 1.20 (m, 2H) ppm. LC/MS (ESI^+) 557.4.

Part C. The product from Part B (250 mg, 0.45 mmol) was stirred in CH_2Cl_2 (2 mL) and TFA (2 mL) at rt for 20 min. The solvents were evaporated. The residue was purified by FCC (silica gel, EtOAc, then EtOAc: MeOH=10:1) to yield the title compound (188 mg, 92%). ^1H NMR ($CDCl_3$) δ 7.55 (d, *J*=8.4 Hz, 2H), 7.45 (d, *J*=9.2 Hz, 4H), 7.36 (d, *J*=8.4 Hz, 2H), 6.91 (d, *J*=8.8 Hz, 2H), 4.15 (t, *J*=6.6 Hz, 2H), 3.80

(s, 3H), 3.17 (t, *J*=6.6 Hz, 2H), 2.50 (s, 3H), 1.56 (m, 2H), 1.12 (m, 2H) ppm. LC/MS (ESI^+) 457.4.

Example 131

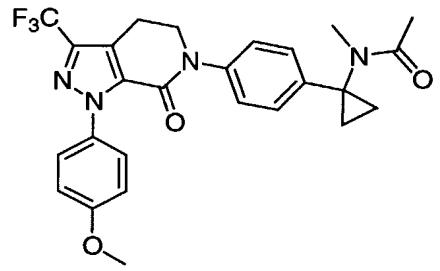
6-[4-(1-Dimethylaminocyclopropyl)phenyl]-1-(4-methoxyphenyl)-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one



The product from Example 130 (30 mg, 0.066 mmol) was stirred in CH_3CN (0.2 mL) at rt under N_2. Aqueous formaldehyde (0.07 mL, 7 mmol, 10 eq) was added followed by the addition of HOAc (0.012 mL, 0.21 mmol, 3.2 eq). The mixture was stirred for 15 min, and then $NaBH_3CN$ (12 mg, 0.198 mmol) was added. The mixture was stirred at rt for 2h. Several drops of acetone were added followed by 1N NaOH. The mixture was extracted with CH_2Cl_2, washed with H_2O and brine, dried over $MgSO_4$, and concentrated to dryness. The residue was purified by FCC (silica gel, EtOAc, than EtOAc: MeOH=10:1) to yield the title compound (15.7 mg, 51%). ^1H NMR ($CDCl_3$) δ 7.46 (d, *J*=8.8 Hz, 2H), 7.29 (m, 4H), 6.92 (d, *J*=9.2 Hz, 2H), 4.15 (t, *J*=6.6 Hz, 2H), 3.81 (s, 3H), 3.16 (t, *J*=6.6 Hz, 2H), 2.28 (s, 6H), 1.02 (m, 2H), 0.81 (m, 2H) ppm. LC/MS (ESI^+) 471.4.

Example 132

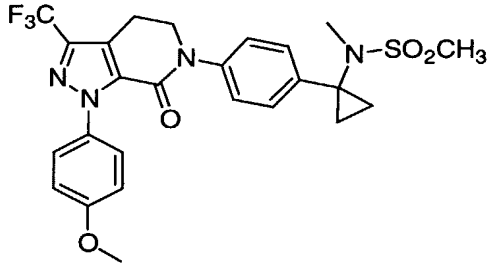
***N*-(1-{4-[1-(4-Methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}-cyclopropyl)-*N*-methyl-acetamide**



Following a procedure analogous to that used for the preparation of Example 93, the title compound was prepared. Silica gel purification yielded the title compound. LC/MS (ESI$^+$) 499.4 (M+H). ^{1}H NMR ($CDCl_3$) δ 7.46 (d, *J*=9.2 Hz, 2H), 7.26 (m, 2H), 6.93 (AA'BB', *J*=8.8, 7.0 Hz, 4H), 4.12 (t, *J*=6.6 Hz, 2H), 3.81 (s, 3H), 3.16 (t, *J*=6.6 Hz, 2H), 3.01 (s, 3H), 2.05 (s, 3H), 1.50 (m, 4H) ppm.

Example 133

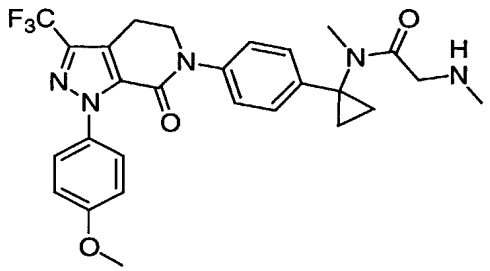
***N*-(1-{4-[1-(4-Methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}-cyclopropyl)-*N*-methyl-methanesulfonamide**



Following a procedure analogous to that used for the preparation of Example 94, the title compound was prepared. Silica gel purification yielded the pure desired product. LC/MS (ESI$^+$) 535.6 $(M+H)^+$.

Example 134

***N*-(1-{4-[1-(4-Methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}-cyclopropyl)-*N*-methyl-2-methylaminoacetamide**

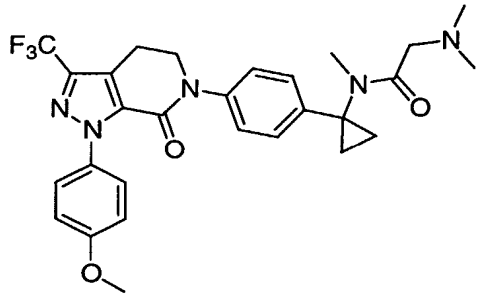


Part A. The product of Example 130 (45 mg, 0.1 mmol) was stirred in CH_2Cl_2 (1 mL) at rt. NaOH (12 mg, 3.0 eq) was added followed by the addition of chloroacetyl chloride (0.015 mL, 2.0 eq). The mixture was stirred at rt for 3h. Additional NaOH (20 mg) and chloroacetyl chloride (0.020 mL) were added. The mixture was stirred at rt overnight. The mixture was extracted with CH_2Cl_2 (2x), washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was used directly in the next step without further purification. LC/MS (ESI^+) 533.6 (M+H), t_R=2.63 min (10-90% CH_3CN in H_2O in a 4-min run).

Part B. The product from part A (15 mg, 0.028 mmol) was stirred in DMF (0.1 mL) in a Pyrex tube under N_2. K_2CO_3 (20 mg) was added, followed by the addition of a solution of $NHMe_2$ in THF (2M, 0.1 mL). The reaction mixture was stirred at 80°C overnight. H_2O was added, and the mixture was extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by FCC (silica gel, CH_2Cl_2, then CH_2Cl_2:EtOAc, then EtOAc:MeOH=10:1) to give the title compound (5.0 mg, yield: 33%). ^1H NMR ($CDCl_3$) δ 7.46 (d, J=8.8 Hz, 2H), 7.29 (m, 4H), 6.92 (d, J=9.2 Hz, 2H), 4.15 (t, J=6.6 Hz, 2H), 3.81 (s, 3H), 3.16 (t, J=6.6 Hz, 2H), 2.28 (s, 6H), 1.02 (m, 2H), 0.81 (m, 2H) ppm. LC/MS (ESI^+) 528.6 (M+H), t_R=2.07 min (10-90% CH_3CN in H_2O in a 4-min run).

Example 135

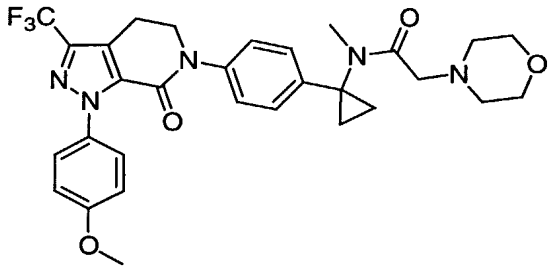
2-Dimethylamino-*N*-(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropyl)-*N*-methylacetamide



Following a procedure analogous to that used for the preparation of Example 134, the title compound was prepared. Silica gel purification yielded the pure desired product. LC/MS (ESI^+) 542.6 (M+H), t_R=2.10 min (10-90% CH_3CN in H_2O in a 4-min run).

Example 136

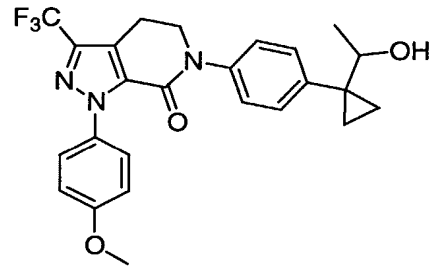
***N*-(1-{4-[1-(4-Methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}-cyclopropyl)-N-methyl-2-morpholin-4-yl-acetamide**



Following a procedure analogous to that used for the preparation of Example 134, the title compound was prepared. Silica gel purification yielded the pure desired product. LC/MS (ESI^+) 584.2 $(M+H)^+$, t_R=2.05 min (10-90% CH_3CN/H_2O in a 4-min run).

Example 137

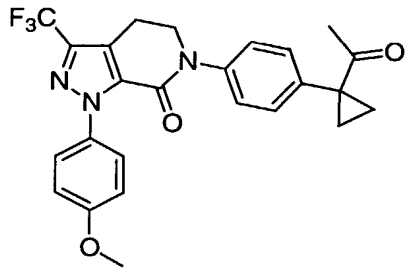
6-{4-[1-(1-Hydroxyethyl)cyclopropyl]phenyl}-1-(4-methoxyphenyl)-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one



1-{4-[1-(4-Methoxy-phenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridin-6-yl]-phenyl}-cyclopropanecarbaldehyde (93 mg, 0.21 mmol) was stirred in Et_2O (2 mL) at -78°C. $ZnMe_2$ (2M in toluene, 0.16 mL, 1.5 eq) was added followed by the addition of $TiCl_4$ (1 M in CH_2Cl_2, 0.3 mL). The resulting mixture was stirred for 1h. The reaction was quenched by addition of NH_4Cl, extracted with EtOAc, washed with H_2O and brine, dried over $MgSO_4$, filter, and concentrated. The residue was purified by silica gel column to yield the pure desired product (62 mg, yield: 64.5%). LC/MS (ESI^+) 472.6 $(M+H)^+$, t_R=2.44 min (35-95% CH_3CN/H_2O in a 6-min run).

Example 138

6-[4-(1-Acetylcyclopropyl)phenyl]-1-(4-methoxyphenyl)-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one

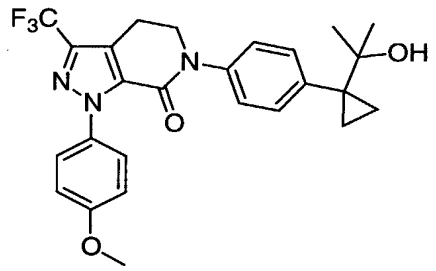


The product from Example 137 (30 mg, 0.063 mmol) was stirred in CH_2Cl_2 (1 mL) at rt under N_2. 4Å molecular sieves

(30 mg) and NaOAc (15.4 mg, 0.187 mmol) were added followed by the addition of PCC (27.5 mg, 0.126 mmol). The reaction mixture was stirred at rt for 1.5 h. The mixture was filtered through Celite®, rinsed with CH_2Cl_2, washed with H_2O, brine, concentrated to dryness. Silica gel purification afforded the title compound. LC/MS(ESI$^+$) 470.6 $(M+H)^+$, t_R=2.77 min (10-90% CH_3CN/H_2O in a 4-min run). ^1H NMR ($CDCl_3$) δ 7.47 (d, *J*=8.4 Hz, 2H), 7.33 (AA'BB', *J*=8.8 Hz, 4H), 6.93 (dd, *J*=8.8, 2.3 Hz, 2H), 4.16 (t, *J*=6.6 Hz, 2H), 3.83 (s, 3H), 3.29 (t, *J*=6.6 Hz, 2H), 2.77 (s, 6H), 1.67 (m, 2H), 1.15 (m, 2H) ppm.

Example 139

6-{4-[1-(1-Hydroxy-1-methyl-ethyl)cyclopropyl]phenyl}-1-(4-methoxyphenyl)-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one



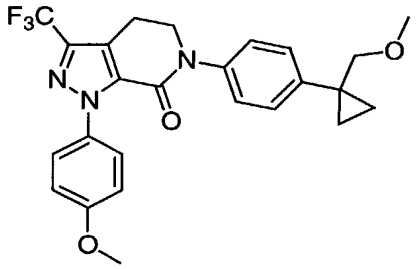
Part A. 1-(4-Iodo-phenyl)-cyclopropanecarboxylic acid methyl ester (0.96 g, 3.17 mmol) was stirred in THF (15 mL) at -78°C under N_2. MeMgCl (3.0 M in THF, 4.2 mL, 4.0 eq) was added dropwise, and the reaction was stirred for 1 h during which period the temperature was raised from -78°C to 0°C. It was quenched by the addition of sat'd NH_4Cl, and extracted with EtOAc (2 x). The organics were washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by FCC (silica gel, hexanes, then hexanes:CH_2Cl_2=1:1 to 0:1) to give 2-[1-(4-iodo-phenyl)-cyclopropyl]-propan-2-ol (0.71 g,

yield: 73.9%). LC/MS(ESI+) 303.4 $(M+H)^+$, t_R=2.57 min (10-90% CH_3CN/H_2O in a 4-min run).

Part B. The product from Part A (102 mg, 0.33 mmol) and (105 mg, 0.34 mmol) were stirred in dry DMSO (0.5 mL). K_2CO_3 (90.5 mg, 2.0 eq) was added followed by the addition of CuI (32 mg, 0.17 mmol) and 1,10-phenanthroline (31 mg, 0.17 mmol). The resulting mixture was heated at 120°C for 3h. After cooling, it was extracted with EtOAc (2x), washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by FCC (silica gel, CH_2Cl_2:EtOAc=1:1, then EtOAc) to give the title compound (95 mg, yield: 59.4%). LC/MS(ESI+) 486.8 $(M+H)^+$, t_R=3.03 min (10-90% CH_3CN/H_2O in a 4-min run).

Example 140

6-[4-(1-Methoxymethylcyclopropyl)phenyl]-1-(4-methoxyphenyl)-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one

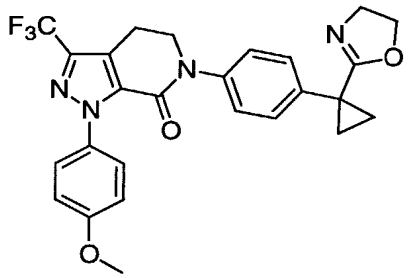


Part A. [1-(4-Iodo-phenyl)-cyclopropyl]-methanol (0.25 g, 0.94 mmol) was dissolved in CH_2Cl_2 (1.5 mL). Proton sponge (0.21 g, 0.97 mmol) was added followed by trimethoxyloxonium tetrafluoroborate (0.15 g, 1.0 mmol). The reaction was allowed to stir for 3 h and was then quenched with H_2O, concentrated, and purified via flash chromatography (silica, 100% EtOAc) to afford the title compound (0.13 g, yield: 47%). ^1H NMR ($CDCl_3$) δ 7.64 (d, J=8.4 Hz, 2H), 7.11 (d, J=8.2 Hz, 2H), 3.65 (d, J=6.2 Hz, 2H), 1.57 (s, 3H), 0.86 (s, 4H) ppm.

Part B. The product from Part A and 1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one were coupled using the usual Buchwald Ullman procedure. LC/MS (ESI^+) 472.6 $(M+H)^+$, t_R=2.98 min (10-90% CH_3CN/H_2O in a 4-min run). ^1H NMR ($(CD_3)_2CO$, 300 MHz) δ 7.49 (d, *J*=9.1 Hz, 2H), 7.29 (AA'BB', *J*=8.8 Hz, 4H), 6.96 (dd, *J*=9.2 Hz, 2H), 4.15 (t, *J*=6.6 Hz, 2H), 3.82 (s, 3H), 3.44 (s, 2H), 3.23 (s, 3H), 3.16 (t, *J*=6.3 Hz, 2H), 0.84 (d, *J*=2.2 Hz, 2H), 0.81 (d, *J*=2.5 Hz, 2H) ppm.

Example 141

6-{4-[1-(4,5-Dihydro-oxazol-2-yl)cyclopropyl]phenyl}-1-(4-methoxyphenyl)-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one



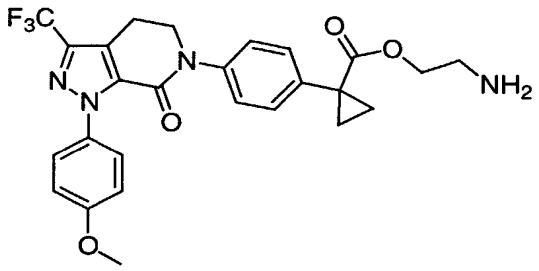
Part A. To a slurry of 1-(4-iodo-phenyl)-cyclopropane-carboxylic acid (0.693 g, 2.41 mmol) in CH_2Cl_2 (3.0 mL) at 0°C was added $(COCl)_2$ (0.40 mL, 4.6 mmol) dropwise. The reaction was warmed to rt and stirred under N_2 for 1 h. The reaction was monitored by LC/MS. Upon completion the reaction was concentrated on the rotary evaporator and diluted with CH_2Cl_2 (3 mL). Ethanolamine (0.30 mL, 4.54 mmol) was added drop-wise and the reaction stirred for 1.5 h. The reaction was then quenched with H_2O and extracted with EtOAc (2x). The organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to dryness. The crude 1-(4-iodo-phenyl)-cyclopropanecarboxylic acid (2-hydroxy-ethyl)-amide was

taken directly to the next reaction without further purification. LC/MS (ESI+) 332.2 $(M+H)^+$, t_R=2.16 min (10-90% CH_3CN/H_2O in a 4-min run). It was dissolved in THF (10.0 mL) and methoxycarbonylsulfamoyl triethylammonium hydroxide inner salt (0.61 g, 2.56 mmol) was added. The reaction was heated to 70°C for 2h and then cooled. The reaction mixture was diluted with EtOAc and washed with H_2O (2x), brine, dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash chromatography (silica, EtOAc: Hexanes 3:1) to 2-[1-(4-iodo-phenyl)-cyclopropyl]-4,5-dihydro-oxazole (0.41 g, yield: 55%). LC/MS (ESI^+) 314.0 (M+H), t_R=1.62 min (10-90% CH_3CN/H_2O in a 4-min run). ^1H NMR ($CDCl_3$) δ 7.65 (d, *J*=8 Hz, 2H), 7.13 (d, *J*=8.4 Hz, 2H), 4.32 (t, *J*=9.5 Hz, 2H), 3.87 (t, *J*=9.1, 9.6, 2H), 1.67 (m, 2H), 1.23 (m, 2H) ppm.

Part B. The product from Part A (75.2 mg, 0.240 mmol) and 1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (76.8 mg, 0.247 mmol) were dissolved in DMSO (0.5 mL). Potassium carbonate (0.109 g, 0.788 mmol), copper iodide (spatula tip), and 1,10-phenanthroline (spatula tip) were added and the reaction was heated to 120°C for 12h under an environment of N_2. The reaction was cooled, diluted with EtOAc, washed with H_2O (2x), brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (silica, 100% EtOAc) afforded the title compound. LC/MS (ESI^+) 497.6 (M+H), t_R=2.44 min (10-90% CH_3CN/H_2O in a 4-min run). ^1H NMR ($(CD_3)_2CO$, 300 MHz) δ 7.51 (d, *J*=9.0 Hz, 2H), 7.32 (AA'BB', *J*=8.4 Hz, 4H), 6.97 (d, *J*=9.0 Hz, 2H), 4.16 (m, 4H), 3.82 (s, 3H), 3.67 (t, *J*=9.2 Hz, 2H), 3.17 (t, *J*=6.6 Hz, 2H), 2.02 (m, 2H), 1.42 (m, 2H), 1.17 (m, 2H) ppm.

Example 142

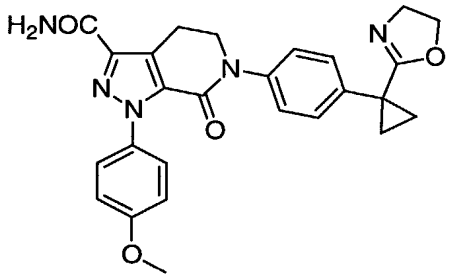
1-{4-[1-(4-Methoxy-phenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridin-6-yl]-phenyl}-cyclopropanecarboxylic acid 2-amino-ethyl ester



A side product resulting from a minor impurity in the starting material of Part C of Example 141 was isolated and characterized to be the title compound. LC/MS (ESI$^+$) 515.6 $(M+H)^+$, t_R=2.22 min (10-90% CH_3CN/H_2O in a 4-min run). ^1H NMR $(CD_3)_2CO$, δ 7.50 (d, *J*=8.8 Hz, 2H), 7.38 (AA'BB', *J*=8.6 Hz, 4H), 7.00 (d, *J*=8.8 Hz, 2H), 4.20, (t, 2H), 3.83 (s, 3H), 3.45 (t, 2H), 3.20 (m, 4H), 1.40 (m, 2H), 0.95 (m, 2H) ppm.

Example 143

6-{4-[1-(4,5-Dihydro-oxazol-2-yl)-cyclopropyl]-phenyl}-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide



Part A. The product of Part A from Example 141 (0.10 g, 0.32 mmol) and 1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid ethyl ester (0.10 g, 0.32 mmol) were dissolved in DMSO (1.5 mL). Potassium carbonate (1.3 g, 0.94 mmol), copper iodide (0.02 g, 0.10 mmol), and 1,10-phenanthroline (0.02 g, 0.11